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Vol. 15 MAY, 1944 No. 5

SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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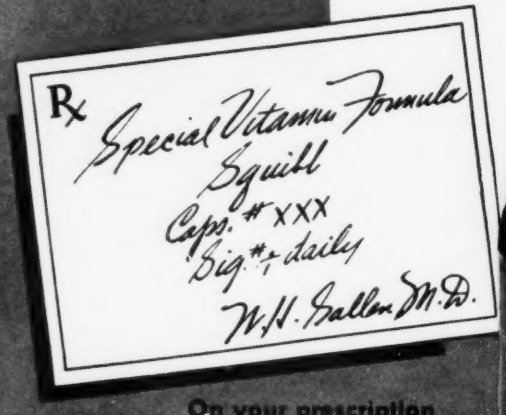

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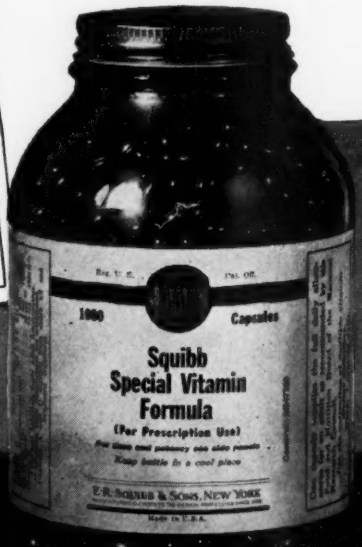

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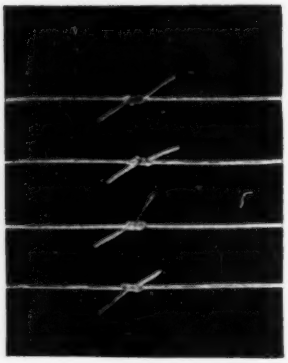

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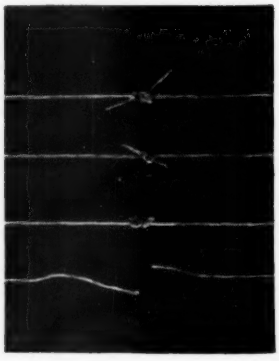

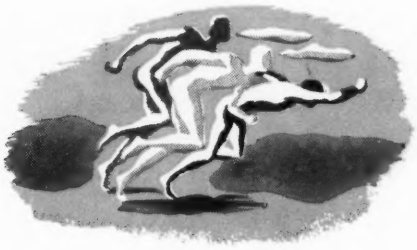

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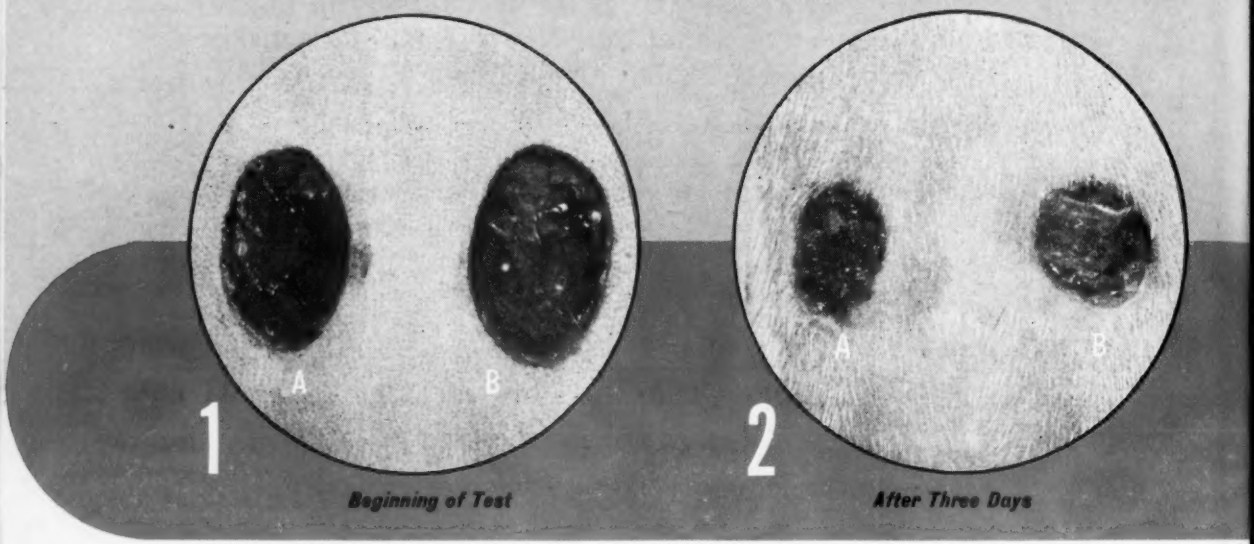

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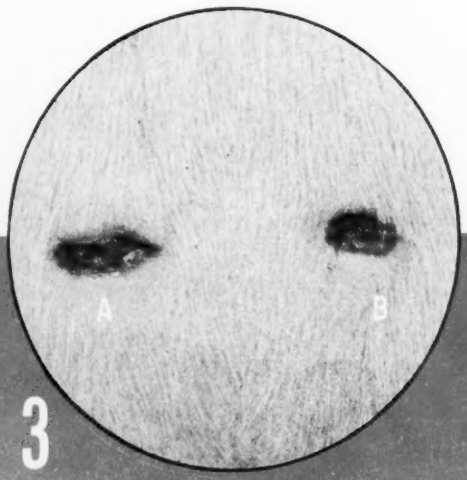

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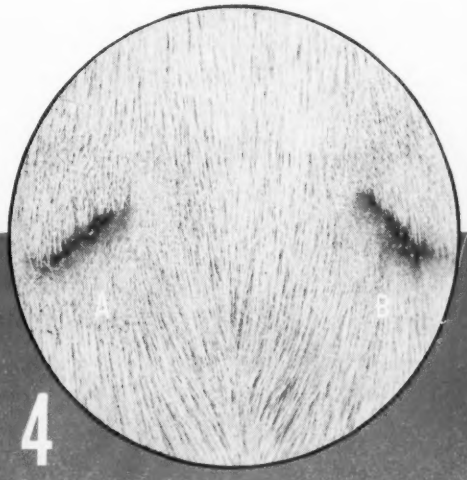

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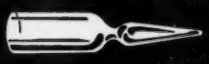

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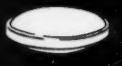

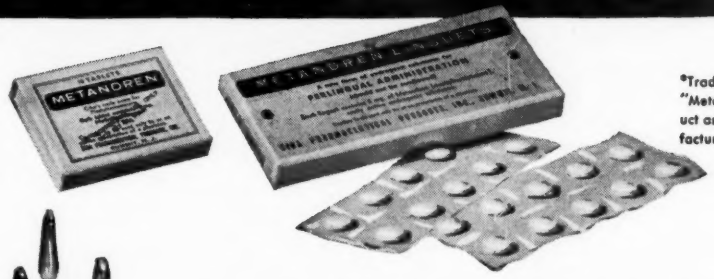

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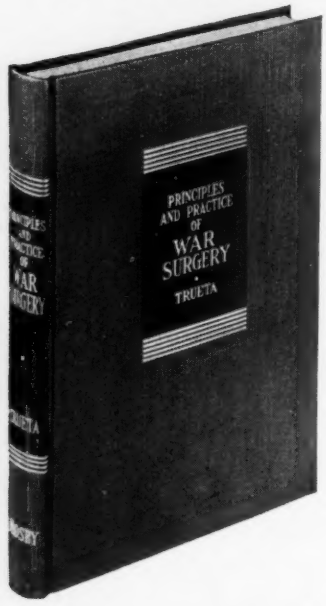

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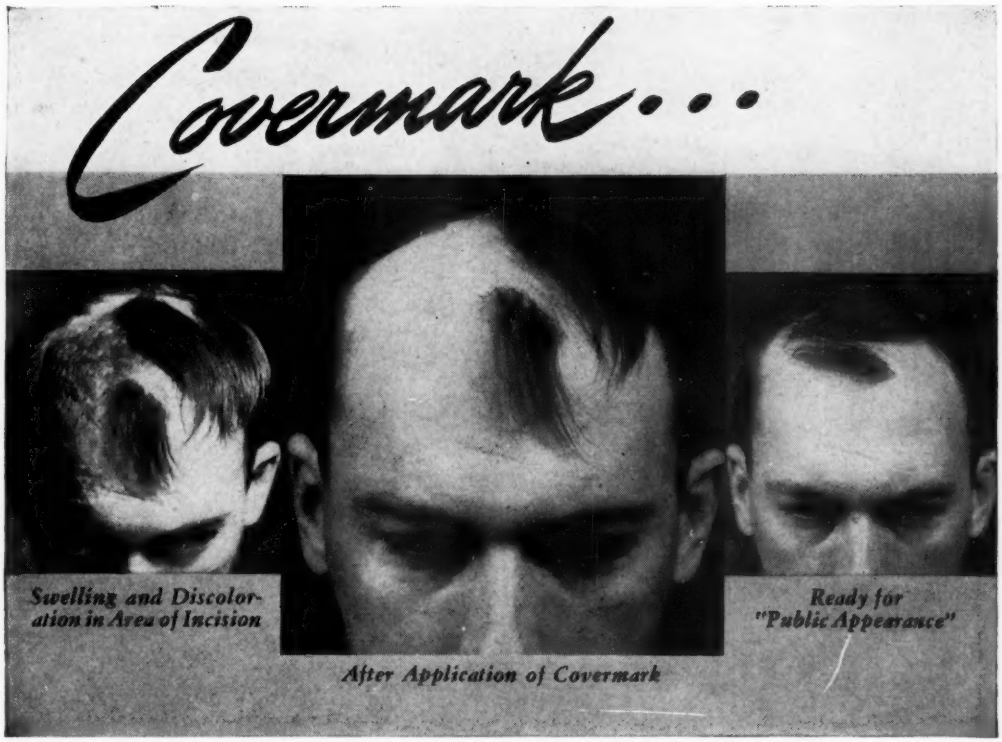
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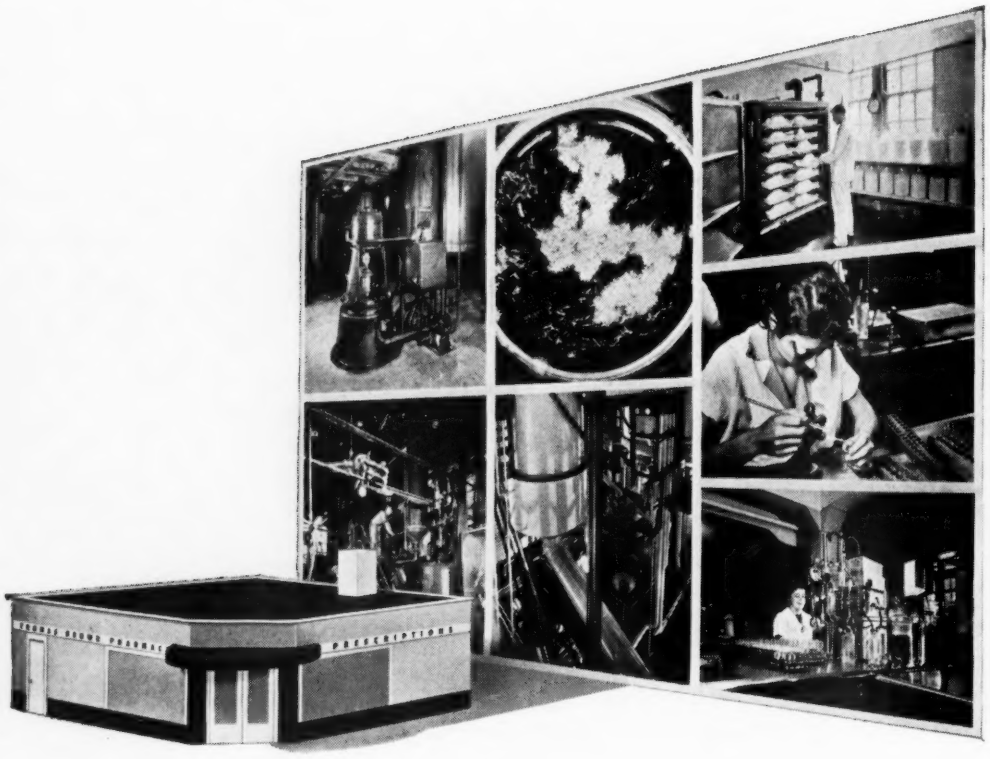

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SURGERY

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HYPERINSULINISM

A REPORT OF THE SURGICAL TREATMENT OF THREE PATIENTS

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THE clinical manifestations of hypoglycemia may vary in individual cases but usually they consist of recurring episodes of some combination of vasomotor, gastrointestinal, neuromuscular, or mental disturbances associated with fasting, hunger, or exercise (Table I). A blood sugar determination below 50 mg. per cent usually is found in the fasting state or during an acute attack. Mild episodes disappear if the patient takes carbohydrate by mouth, but severe prolonged attacks associated with coma and convulsions may require the administration of glucose solution intravenously. Individual tolerance to hypoglycemia varies and very mild attacks may disappear spontaneously. Hyperinsulinism is only one of the causes of this state (Table II), and the other possible sources should be eliminated as completely as is possible by clinical and laboratory studies before a diagnosis of hypoglycemia caused by hypersecretion of pancreatic islet cells is made. Recently a considerable number of cases of hypoglycemia resulting from hyperinsulinism have been reported in the literature (Table III).

In 1943, three patients with this condition were treated on the surgical service at the University of California Hospital.

CASE 1.—J. F. N., a man 57 years of age, had had, for about one year, frequent attacks characterized by vertigo, blurred vision, diplopia, weakness, sweating, mental confusion, and convulsive movements. These attacks came early in the morning or just before mealtime, the usual duration being about thirty minutes.

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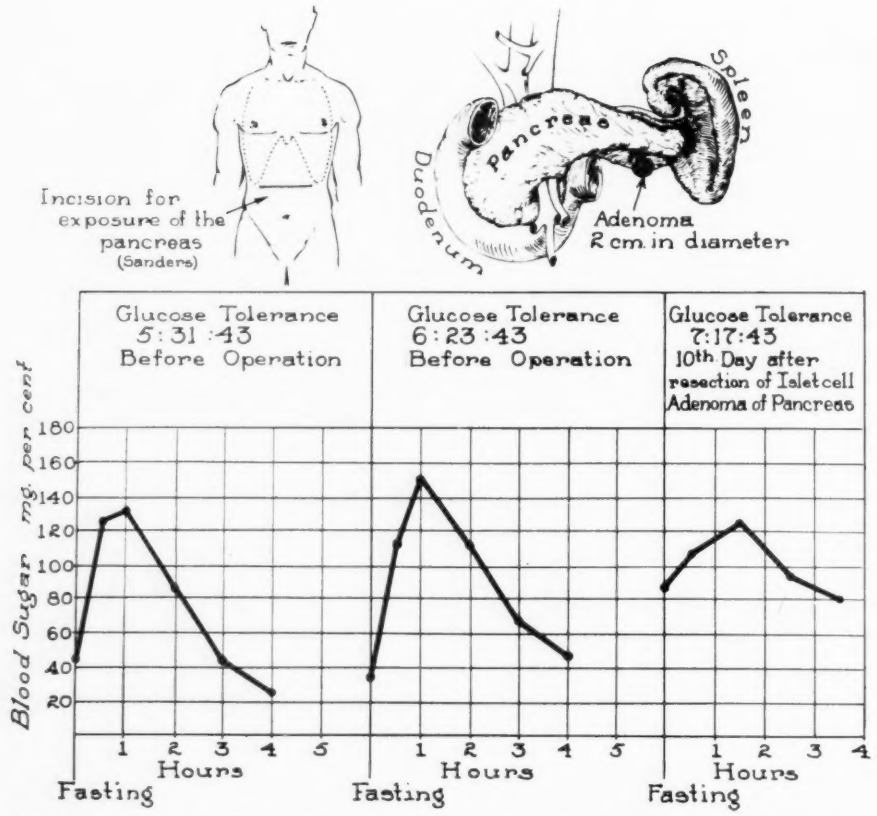

Fig. 1 (Case 1).—Diagrams illustrating incision for exposure of the pancreas, location of islet-cell adenoma of the pancreas, and glucose tolerance tests taken before and after resection of an islet-cell tumor of the pancreas.

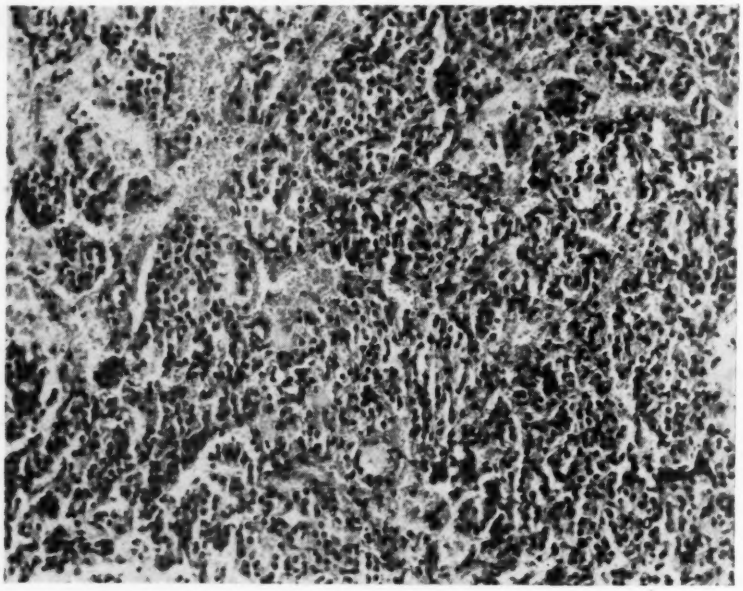

Fig. 2 (Case 1).—Photomicrograph of a typical field of an islet-cell adenoma of the pancreas. (×120.)

TABLE I

CLINICAL MANIFESTATIONS OF HYPOGLYCEMIA

Sweating	Occurs in attacks
Pallor	
Tremor	Related to:
Vertigo	1. Meals—i.e., fasting
Blurred vision; diplopia	2. Exercise
Nervousness and weakness (especially when hungry)	
Fatigue, malaise, lassitude	Relieved by taking CHO (unless severe and greatly prolonged)
Apprehension; fear	
Mental confusion	
Dysarthria	
Disorientation	Mental deterioration in long untreated cases
Inability to arouse from sleep in morning; drowsiness	
Convulsions	
Collapse, shock	Individuals vary in tolerance to low blood glucose
Similarity to psychoses, neuroses	
Irrationality; psychomotor activity; maniacal states	
Hunger (may simulate pains of peptic ulcer)	
Tachycardia	May be aggravated by other acute conditions
Elevation of blood pressure	
Low fasting blood sugar	

Whipple's Triad of Symptoms in Hyperinsulinism

1. Attacks of nervous or gastrointestinal disturbances coming on in fasting state associated with a
2. Hypoglycemia with blood glucose readings below 50 mg. per cent and
3. Relieved immediately by ingestion of glucose

He always felt well after eating. Frequent feedings with carbohydrate increased the interval between the attacks. During his stay in the hospital a convulsion occurred in the early morning but was controlled promptly by the administration of carbohydrate. The results of fasting blood sugar determinations and glucose tolerance tests are seen in Table V and Fig. 1. Physical examination showed no significant findings.

A diagnosis of hyperinsulinism was made and exploration of the pancreas was performed on July 6, 1943. A spherical, vascular, dark red tumor, 2 cm. in diameter, lay adjacent to the inferior border of the tail of the pancreas (Fig. 1). Its gross appearance was similar to that of a hemolymph node or an accessory spleen. The tumor appeared to be entirely encapsulated but microscopically the capsule was seen to be incomplete and there was a small area of attachment to normal pancreatic tissue. Large vascular channels traversed the parenchyma of the tumor, which consisted of cells having the appearance of those of islets of Langerhans (Fig. 2). The pathologist's diagnosis was adenoma of the islets of Langerhans.

The patient was completely relieved of symptoms of hypoglycemia after operation. Postoperative fasting blood sugar determinations and glucose tolerance tests are shown in Table V and Fig. 1.

CASE 2.—T. F., a woman 62 years of age, had had generalized convulsions for twelve years. Usually the episodes occurred several hours after a meal and often were preceded by nervousness, faintness, weakness, vertigo, sweating, and a feeling of anxiety. The interval between attacks varied from two days to three weeks. The patient also had a history of cholecystitis and this diagnosis had been confirmed elsewhere by x-ray studies. Her behavior indicated some evidence of mental

TABLE II

CONDITIONS THAT MAY BE ASSOCIATED WITH HYPOGLYCEMIA

Hyperinsulinism—islet-cell tumor, hypersecretion
Pituitary—anterior lobe deficiency
Adrenal—cortical deficiency
Thyroid—myxedema
Thymus—hypertrophy of
Liver—injury due to disease
Autonomic nervous system—rare disorders
Certain psychoses and neuroses—rare
Effort—athletes
Lactation
Low renal threshold for glucose—and low CHO intake

TABLE III

CASES OF HYPERINSULINISM RECORDED IN THE LITERATURE

Tumors of the Islets of Langerhans:	
Benign adenomas	128*
Questionably malignant (Whipple)	22
Malignant tumors	14
Total number of tumors	164
Hypersecretion of the Islets of Langerhans:	
Hyperplasia	8
"Adenomatous" hyperplasia (Orr)	1
Pancreatitis	1
Normal	26
Not designated	3
Total cases of hypersecretion	39
Total cases of hyperinsulinism	203

*Extrapancreatic in five cases.

TABLE IV

LOCATION OF ABERRANT PANCREATIC TISSUE
(FAUST AND MUDGETT)

LOCATION	NO. OF CASES
Stomach	95
Duodenum	105
Duodenojejunal angle	2
Jejunum	65
Ileum	18
Small intestine (not located)	6
Diverticulum of stomach	3
Diverticulum of duodenum	7
Diverticulum of jejunum	1
Diverticulum of ileum	8
Diverticulum of small intestine	2
Meckel's diverticulum	21
Diverticulum (not located)	1
Umbilical fistula	1
Mesentery	3
Omentum	4
Splenic capsule	3
Spleen	1
Gall bladder	3
Cystic duct	1
Gastrocolic ligament	1
Transverse mesocolon	1
Location questionable	18
	370

TABLE V (CASE 1)

FASTING BLOOD SUGAR DETERMINATIONS

DATE	BLOOD SUGAR (MG. %)	REMARKS
5/31/43	43	
6/18/43	55	
6/21/43	45	
6/23/43	35	
6/24/43	46	
7/ 6/43		Operation
7/ 9/43	133	
7/17/43	88	

TABLE VI (CASE 2)

FASTING BLOOD SUGAR DETERMINATIONS

DATE	BLOOD SUGAR (MG. %)	REMARKS
2/25/43	38	
3/12/43	38	During a seizure
3/15/43	50	
3/26/43	40	During a seizure
3/27/43	31	During a seizure
3/29/43	37	
4/ 2/43		Cholecystectomy
4/ 3/43	69	
4/ 6/43	50	
4/ 8/43	46	
4/ 9/43	49	
4/10/43	62	
4/14/43	61	
4/15/43	69	
5/ 3/43	70	
5/20/43	69	
8/16/43	50	
9/16/43		Islet tumor removed
9/21/43	110	
9/28/43	97	
10/ 7/43	104	
10/ 8/43	95	
11/ 7/43	109	

deterioration. Several seizures occurred while the patient was in the hospital and were relieved promptly by means of glucose therapy. The fasting blood sugar determinations and glucose tolerance tests are shown in Table VI and Fig. 3.

Laparotomy was performed on April 2, 1943. A distended, inflamed gall bladder was removed. A large indurated mass was felt in the tail and body of the pancreas and the possibility of acute pancreatitis was suspected. Following the cholecystectomy no convulsive seizures were experienced but the patient continued to have episodes of weakness, vertigo, nervousness, and sweating. Four weeks after operation the patient suffered pain in the right upper quadrant of the abdomen, nausea, vomiting, and jaundice which subsided with medical treatment.

A second laparotomy was performed on Sept. 18, 1943. A vascular tumor 7.5 by 5.5 by 4.5 cm. was excised from the tail of the pancreas (Fig. 3). The color of the tumor varied from pink to deep red and purple, the capsule was intact, and the parenchyma was lobular with varying pattern. In many areas there were slender spiral cords of cubical epithelial cells with small vascular channels between them. In some areas the cells were closely packed and in others there were small groups of cells having the appearance of islands of Langerhans (Fig. 4). A few groups of

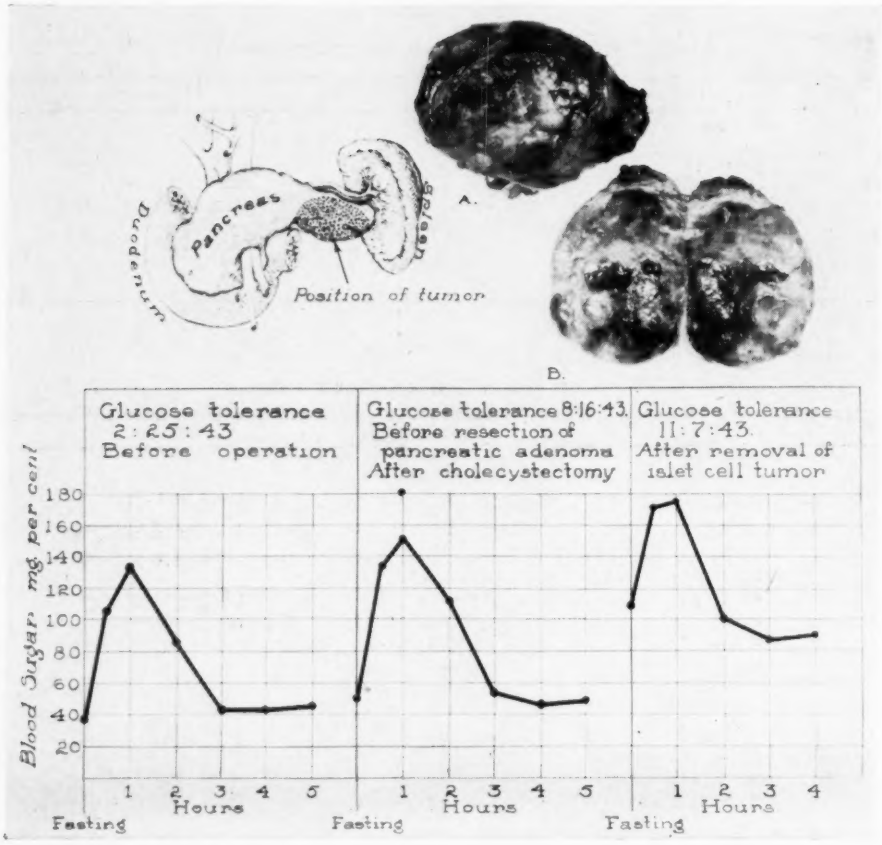

Fig. 3 (Case 2).—Diagram indicating location of the tumor and photomicrograph made of the islet-cell adenoma following its removal from the pancreas. Glucose tolerance tests made before and after removal of the tumor.

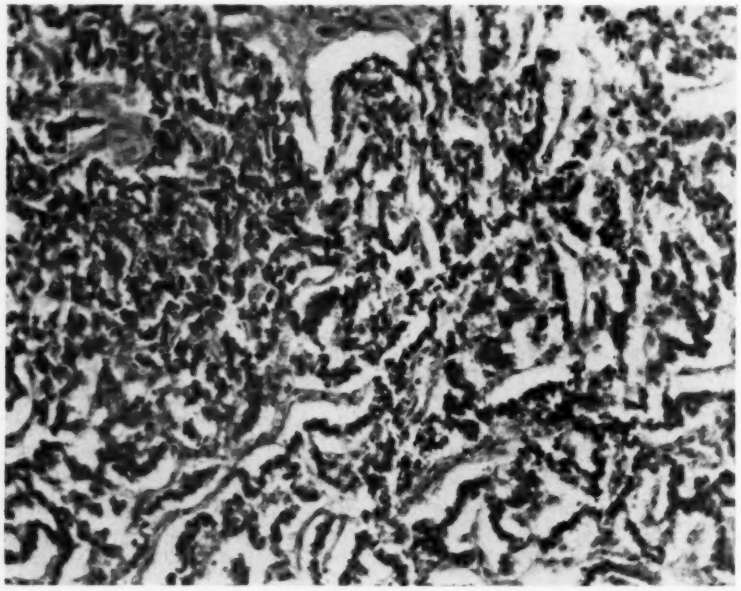

Fig. 4 (Case 2).—Photomicrograph of islet-cell adenoma of the pancreas. (×120.)

islet cells apparently lay within vessels. The pathologist's diagnosis was adenoma of the islet cells of the pancreas. The patient's postoperative course was uneventful and there have been no hypoglycemic symptoms since the resection of the pancreatic adenoma.

CASE 3.—M. S., a girl 19 years of age, had diabetes mellitus that had required dietary management and insulin for at least seven years. Prior to July, 1943, she was on a diet consisting of 125 Gm. of carbohydrate, 80 Gm. of protein, and 85 Gm. of fat. Her daily requirement of insulin was 37 units of protamine insulin and 20 units of regular insulin. On this regime she felt well but occasionally had a reaction to insulin that was relieved by taking sugar. In July, 1943, the hypoglycemic reactions became more frequent. Soon they occurred daily and within a week after their onset the use of insulin had been completely discontinued without affecting the reactions. On a diet consisting of 175 Gm. of carbohydrate, 125 Gm. of protein, and 150 Gm. of fat she was considerably improved but still awakened frequently in the early morning hours with sweating, nervousness, convulsions, and other symptoms characteristic of reaction to insulin. These seizures were relieved by taking carbohydrate in the form of cubes of sugar. Several severe hypoglycemic attacks occurred while the patient was in the hospital. She recovered from each episode promptly when glucose solution was given intravenously. Table VII and Fig. 5 show the fasting blood sugar determinations and glucose tolerance tests. The result of the intravenous hippuric acid test on Sept. 29, 1943, was 1.40 Gm. in one hour.

Exploration of the pancreas was performed on Oct. 6, 1943. No evidence of tumor or aberrant pancreatic tissue could be found. The tail and body of the pancreas were resected to the site of the crossing of the superior mesenteric vessels (Fig. 5). The specimen of pancreas that was excised weighed 15 Gm. On microscopic examination the acinar tissue was seen to be somewhat pale and eosinophilic in some areas and there were numerous collections of large pale cells that were believed to be either enlarged islets of Langerhans or irregularly staining groups of acinar cells. In these areas the islet and acinar tissues were not differentiated so clearly as in normal pancreas. There also were areas in which scattered small islets containing spindle-shaped cells and pyknotic nuclei were seen (Fig. 6). Following the partial resection of the pancreas the patient returned to the condition of diabetes mellitus which is controlled by dietary measures and the administration of insulin.

TABLE VII (CASE 3)

FASTING BLOOD SUGAR DETERMINATIONS

DATE	BLOOD SUGAR (MG. %)	URINE SUGAR	REMARKS
9/28/43	47		No insulin
9/29/43	36	Green reduction	During a seizure
9/30/43	86	Orange (glucose i.v.)	During a seizure
10/ 4/43	26	Blue	
10/ 5/43	28	Blue	
10/ 6/43			Partial resection of pancreas
10/ 7/43	232	Orange reduction	Insulin started
10/ 8/43	250	Red reduction	On insulin
10/10/43	216	Brick reduction	On insulin
10/12/43	169	Green reduction	On insulin
10/16/43	43	Blue	Insulin reaction
11/29/43	39	Blue	On insulin
1/15/44	170		On insulin (evening dose of protamine insulin reduced)

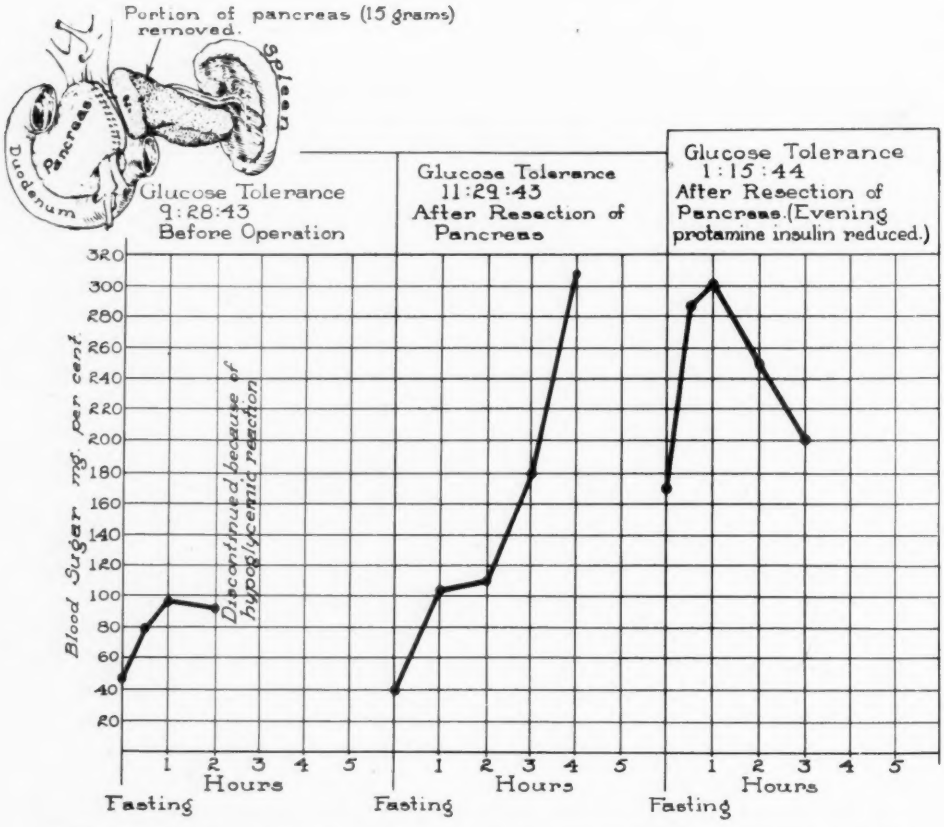

Fig. 5 (Case 3).—Diagram illustrating the amount of pancreas removed and the glucose tolerance tests taken before and after partial resection of the pancreas. This patient had diabetes mellitus, developed hyperinsulinism, and became diabetic again following operation.

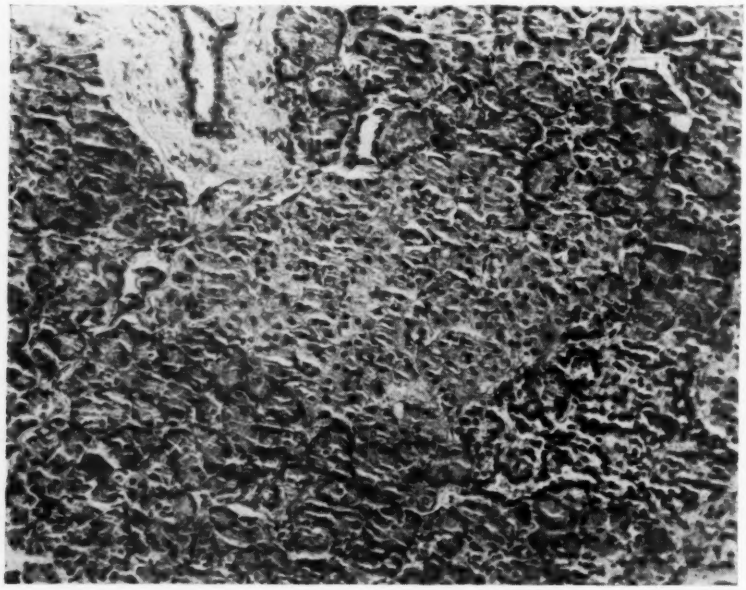

Fig. 6 (Case 3).—Photomicrograph of a field showing one of the small islets of Langerhans and also one of the larger areas of faintly staining cells that may be a hyperplastic island of Langerhans. (×120.)

Hyperinsulinism may be caused by tumors containing actively secreting islet cells or by the hypersecretion of insulin in a pancreas in which the islets of Langerhans may appear to be either normal or increased in size and number. Aberrant pancreatic tissue (Table IV) also is a possible source. Rarely, hyperinsulinism has appeared in patients who previously had diabetes mellitus.

The clinical manifestations of hyperinsulinism do not appear in all patients with tumors of the islet cells. Such tumors may be found at autopsy or during laparotomy for other abdominal conditions. It is supposed that insulin is elaborated by the beta cells of the islets of Langerhans and that tumors of the islet cells giving clinical manifestations of hyperinsulinism contain appreciable numbers of these cells. The available methods for staining the granules supposedly typical of the beta (insulin producing) islet cells are not entirely satisfactory, however, so that, histologically, it is not possible to distinguish accurately between the active and the inactive tumors of the islet cells. The microscopic appearance of the cells in these tumors often resembles that of the cells of normal pancreatic islands of Langerhans. They may be arranged in cords, ribbons, or rounded masses, or may assume a rosette or alveolar pattern that usually surrounds a central capillary. The general pattern may be uniform or lobulated. The connective tissue stroma and the capsule vary in thickness and occasionally extensive fibrosis and even calcification are described. Sometimes encapsulation may be incomplete. Mitoses are rare in most tumors. The vascular channels are numerous and occasionally tumor cells are seen in them.

It may be difficult to determine by histologic methods the malignancy or benignancy of tumors of the islet cells. The presence of metastases which usually appear in the regional lymph nodes or liver probably is the only positive sign of malignancy, although lack of complete encapsulation and evidence of invasion of blood vessels by tumor cells have been considered to be histologic evidence of possible malignancy. Hypoglycemia has been induced in rabbits by injecting extracts prepared from active tumors of the islet cells or from the metastases from a malignant tumor of this type.

The dietary management of patients with hypoglycemia consists of low carbohydrate, high protein, high fat food given at frequent intervals (six meals a day). Carbohydrate may be used to relieve acute episodes of hypoglycemia but probably should not be given frequently in large quantities to patients with possible hyperinsulinism because it increases the amount of insulin that is elaborated and also causes the patient to become obese. A diet high in protein and fat insures a prolonged and more uniform supply of available carbohydrate. In patients with hypoglycemia caused by hyperinsulinism, dietary regulation is not likely to be permanently successful. Because of the possibility of malignant change in the tumor, mental deterioration from

prolonged hypoglycemia, or injury during hypoglycemic convulsions, surgical exploration of the pancreas is indicated if the hypoglycemia is considered likely to be the result of hyperinsulinism.

An intravenous infusion of 5 per cent glucose in water is given before and during the operation. A long transverse upper abdominal incision (such as that described by Sanders), in which the rectus muscles are retracted or divided if necessary, gives suitable exposure for exploration of the entire pancreas, but a longitudinal incision may be adequate, particularly if the patient is thin. Often tumors of the pancreatic islet cells arise in the body or tail of the pancreas, but only occasionally are they found in the head of this gland. Multiple tumors have been observed. The entire pancreas, therefore, including the posterior aspect of the head, should be examined carefully even though a tumor is found in the body or tail. Extrapancreatic adenomas of the islet cells are rare but always should be sought during exploration of patients with hyperinsulinism.

Tumors of the islet cells are very vascular. The color varies from yellow or pink to deep red or purple. Usually the neoplasm is small (about 2 cm. in diameter), although a few larger ones have been described, and can be excised completely with some of the contiguous normal pancreas. Large pancreatic ducts should be ligated if it is necessary to divide them during the operation. In some cases it may be necessary to resect a part of the pancreas (the tail, for example) in order to remove the tumor. The defect in the pancreas may be repaired with a few nonabsorbable sutures. Soft rubber drains usually are placed adjacent to the site of excision of a tumor or division of the pancreas, and are brought out of the abdomen through a small separate incision. If, after careful exploration, no tumor of the pancreas or evidence of aberrant pancreatic tissue can be discovered in cases of hyperinsulinism, resection of the pancreas is indicated. David demonstrated the necessity for resection of almost the entire pancreas (leaving only a very small part of the gland) to obtain a satisfactory result in these cases. Such a resection may remove enough hypersecreting islet tissue to relieve the manifestations of hyperinsulinism or may include small tumors that have been overlooked. The radical operation should not be done until the entire pancreas and all locations in which aberrant pancreatic tissue may occur have been searched for adenoma.

SUMMARY

Recently three patients with hyperinsulinism have been observed on the surgical service at the University of California Hospital. Symptoms suggesting hypoglycemia were present in all three and the minimum fasting blood sugar determinations were considerably below 50 mg. per cent. Solitary tumors of pancreatic islet cells were excised from the region of the tail of the pancreas in two of the patients. In one of

these the tumor was almost completely extrapancreatic. Its gross appearance was similar to that of an accessory spleen or hemolymph node and although it was adjacent to the inferior aspect of the pancreas, its attachment to this organ was apparent only on microscopic examination of the specimen.

The third patient was known to have had diabetes mellitus for seven years. Episodes of hypoglycemia appeared and became progressively more frequent and severe over a period of a few weeks. At operation no evidence of tumor or aberrant pancreatic tissue could be found. A partial resection of the pancreas was performed. The condition of diabetes mellitus recurred following the operation and subsequently the patient has remained diabetic. Pathologic examination of the part of the pancreas excised showed alterations in the staining of the tissue suggesting the presence of islets of Langerhans that were increased in number and size.

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THE IMPLANTATION OF THE PANCREATIC DUCT INTO THE GASTROINTESTINAL TRACT

Experimental and Clinical Study*

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ANY discussion of the reimplantation of the pancreatic ducts cannot be more appropriately opened than by the quotation of the short descriptive paragraph by Halsted (1899)[1] narrating the first successful, recorded instance of the operative removal of a carcinoma of the ampulla of Vater performed on Feb. 14, 1899.

> To give the growth a wide margin, a large piece of duodenum was excised, a wedge-shaped piece with the apex at the mesenteric border of the intestine. About three-quarters of an inch of the common duct and a shorter piece of the pancreatic duct were excised. The wound in the duodenum was closed in the usual way with mattress sutures. This was practically an end-to-end anastomosis of the duodenum. The common duct and pancreatic duct were transplanted into the duodenum along the line of suture.

In the preceding year, Codivilla (1898)[2] excised the duodenum and the head of the pancreas in a one-stage procedure similar to that used by Trimble, Parsons, and Sherman in 1941.[3] The pancreatic duct was ligated. No attempt was made to re-establish the communication between the gland and the gastrointestinal tract. A two-stage method was suggested by Sauvé in 1908,[4] but the present interest in the surgery of the pancreas followed the description of a two-stage operation by Whipple, Parsons, and Mullins in 1935,[5] with a report of three applications of the procedure. A brief summary of these developments is presented by Gray and Sharpe (1943).[6] In these procedures, the pancreatic duct was merely ligated without attempting to re-establish drainage of the external secretion of the gland into the alimentary tract.

Exclusion of the external secretion of the pancreas per se from the alimentary tract does not always result in disturbances of fat digestion. Neither has deposition of fat in the liver been constantly observed following atrophy of the acinar tissues of the pancreas. The inconsistency of these manifestations cannot always be explained and has led to confusion as well as conflicting opinions. Much of this confusion probably has arisen because of slight, unrecognized differences in ex-

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*A large portion of the experimental work was done while the author was a Fellow of the National Research Council in Medicine, 1932-34.

periments presumed to be identical or because of the possible presence of aberrant pancreatic tissue. MacCallum, in 1909,[7] pointed out some difficulties to be encountered even when complete ablation of the pancreas is attempted. This view is best stressed by direct quotation:

> . . . Nor was the result of the operation for the extirpation of the pancreas an absolutely clean one, for at the autopsy there were found about the duodenum two minute fragments of pancreatic tissue in good state of preservation and evidently undergoing hypertrophy. The larger of these was about 3 mm. in diameter, and had apparently reformed itself about the

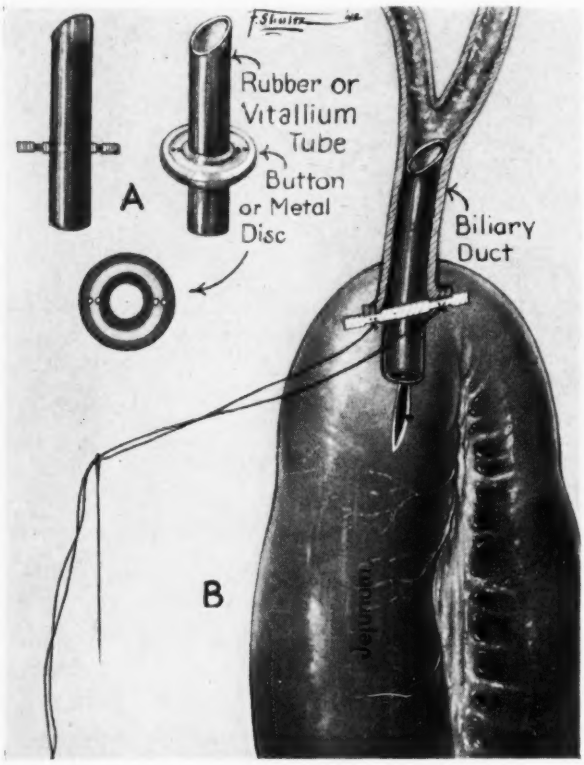

Fig. 1.—Implantation of biliary ducts. *A*, A simple assembly to be used as a cannula for reimplanting biliary ducts into the bowel. *B*, Illustrating the cannula tied into the duct. The traction sutures are threaded onto a long straight needle.

> stump of the duct. The other much smaller fragment had grown in the substance of the wall of the intestine so as to have been quite inaccessible at the time of operation. This minute fragment, too, sent duct-like structures into the intestinal mucosa, but such infinitesimal portions of a large organ like the pancreas seem hardly sufficient to obscure the results of the experiment. Indeed, they were discovered only by microscopical examination. It would be necessary, however, in order to prevent such an occurrence, to resect the portion of the intestine with which the pancreas comes into relation. . . .
>
> The condition of the stools is, however, of interest, for although for a time after the extirpation of the secreting portion of the pancreas, they became very voluminous and on certain days consisted almost entirely of fat,

they later became quite normal in appearance. During the whole of the last two weeks of the animal's life, the food consisted of beefsteak which contained a good deal of fat; but although there were sometimes evidences of incomplete digestion of the beef, the stools did not again assume the vaseline-like consistency which they showed a short time after the extirpation of the pancreas. One receives the impression that here, too, a compensatory process is brought about, through which the fat-splitting action of the pancreatic juice is gradually replaced by a similar ferment produced elsewhere, probably in the intestine itself.

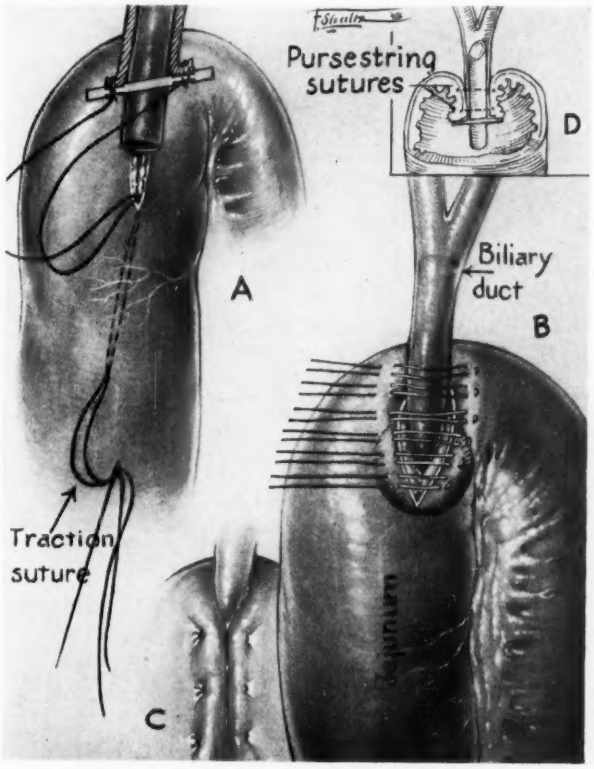

Fig. 2.—Implantation of biliary ducts. *A*, Illustrating the passage of the traction sutures through the opening in the bowel and out on the opposite side. In practice, the traction sutures are not passed until after the closing mattress sutures shown in *B* have been placed. The continuation of the incision in the bowel down to the submucosa only is covered by the cannula and is not visible.

B, Showing the cannula and duct drawn into the bowel. The traction sutures have been cut short and allowed to retract into lumen of the bowel. This last step is best done after the mattress sutures have been tied as in *C*.

C, The completed anastomosis. *D*, Demonstrating the procedure when the duct is anastomosed into the end of a segment of bowel. Two purse-string sutures close the bowel around the cannula.

Experimental Reimplantation of Pancreatic Ducts Into the Alimentary Tract.—In 1933 I applied a procedure for the anastomosis of the biliary ducts and bowel[8] (Figs. 1 and 2) to the transplantation of the pancreatic ducts experimentally to various levels of jejunum and ileum of the dog (Fig. 3). It was found that the pancreatic duct invariably grew into the new site and remained patent with free delivery of pancreatic secretion into the bowel. In addition, however, a strong tend-

ency existed for the duct system to re-establish its anastomosis into the duodenum at the site of the original entrance of the duct of Wirsung. Even though the defect in the duodenal wall was inverted with silk and omentum was placed between the duodenum and pancreas at this point, it was found that not only had the duct grown into the bowel at the point of reimplantation, but that one of the small branches of the duct had grown into the duodenum to re-establish this opening

Fig. 3.—An x-ray of pancreas of the dog to show the duct system injected with BiOCl suspension one month after implantation of the duct of Wirsung into the distal ileum. The pancreas is normal microscopically.

with the result that the external pancreatic secretions entered at both sites. In addition, the duct of Wirsung was resected and ligated, and the intramural portion of the duct was excised with a wedge of duodenum. The incision in the duodenum was then closed with interrupted, fine, black silk in two layers. The duct of Santorini was not disturbed. Two weeks later the experiment was terminated and the pancreatic ducts cannulated in the tail of the gland and injected with

India ink. The duct of Wirsung had reestablished its communication with the duodenum at the site of the closure in one-half of the experiments.

Following these transplantations, the pancreas might be soft and entirely normal, or it might be somewhat indurated and show some fibrosis. If the stoma where the duct was implanted into the bowel was examined and found to be somewhat indurated and not covered by pliable, normal mucosa, the pancreas would be firm and fibrotic. In those instances where the pancreas was of normal consistency, the outlet was soft and the mucosa grew to the very edge of the opening. This latter arrangement prevented the reflux of intestinal contents up the pancreatic duct system during periods of increased intraintestinal pressure accompanying peristaltic contractions. In an attempt to ensure an efficient check-valve of mucosa at the stoma, the duct was carried through the bowel wall diagonally to form a channel a few millimeters long just on the submucosa, and the duct was firmly tied to the shaft of the cannula just behind the flange. This tie prevented leakage of digestive ferments into the anastomotic bed by directing the pancreatic secretions through the stem of the cannula beyond the flange. This procedure permits healing with a minimum of necrosis of the tissues of the anastomotic bed and subsequent scar formation and contracture (Fig. 4).

The x-ray reproduced in Fig. 3 is that of a pancreas the duct of which was injected with a BiOCL suspension[9] one month after the experimental transplantation of the duct of Wirsung into the ileum. The pancreas was normal both macroscopically and microscopically.

Application of Procedure to the Transplantation of the Pancreatic Duct in Man.—Recently the opportunity presented itself for the use of this method in the implantation of the pancreatic duct following resection of the head of the pancreas.

CASE REPORT

W. E. W. (J. S. H. No. 83490), a white man, aged 72 years, was first admitted to the John Sealy Hospital on Sept. 29, 1943, complaining of biliary fistula since an operation performed elsewhere on March 17, 1943. For thirty years the patient had not eaten rich pastries or fatty or highly spiced foods because of indigestion and pain characteristic of cholecystitis with cholelithiasis—no jaundice. Suddenly chills and fever were experienced, February, 1943, followed by visible jaundice two days later. On March 25, 1943, the eighth postoperative day, the wound disrupted and a biliary fistula developed. On several occasions the fistula ceased draining, accompanied by chills, fever, and jaundice.

Physical Examination.—Temperature, 98.6° F.; pulse, 78; respirations, 18; blood pressure, 110/74.

There were no significant abnormalities found in the course of the general physical examination except a sinus 2 cm. below the costal margin and 5 cm. to the right of the midline draining golden yellow bile, and bilateral, complete, indirect, inguinal hernia. The patient was slightly jaundiced.

Laboratory Studies.—

Blood: Hemoglobin, 16.6 Gm.; red blood cells, 5.1 million; white blood cells, 10,200; differential, polymorphonuclears, 78; lymph, 22; prothrombin time, patient, 1 minute; control, 58 seconds; coagulation time (Lee & White), 5 minutes; bleeding time, 3 minutes; glucose, 98 mg. per cent; ichteric index, 36.

Urine: Specific gravity, 1.016; alkaline reaction; albumin, negative; sugar, negative. Microscopic examination negative, urobilinogen negative.

Stools: Negative for bile.

Roentgenologic Examination: Gastrointestinal x-ray series, negative. Flat plate of abdomen, negative.

Operation.—

Preoperative Diagnosis: Biliary fistula, common duct obstruction.

Operative Diagnosis: Biliary fistula, common duct obstruction; carcinoma probably arising from the common duct in the head of the pancreas; multiple adhesions.

Operation: Oct. 8, 1943, Exploratory laparotomy; division of multiple adhesions, between the stomach, gall bladder, liver and duodenum; partial resection of stomach;

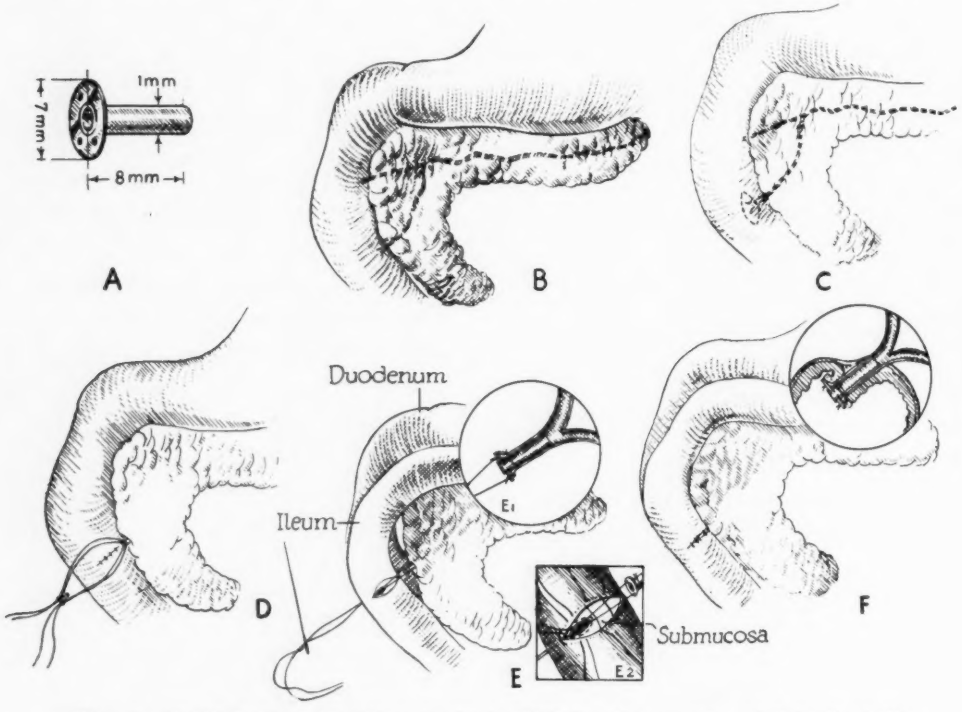

Fig. 4.—Modified from drawings made in 1933 for the experimental implantation of the duct of Wirsung of the dog into the jejunum and ileum.

A, Small silver cannula used in the transplantation.

B, A schematic illustration of the pancreas and its duct system in the dog.

C, The duct of Wirsung is resected and the intramural portion of the duct is excised.

D, The duodenum is closed transversely, and the traction sutures have been placed in the cut end of the duct and passed through the flange of the cannula.

E, The traction sutures are shown passed through the incision in the bowel and on out the opposite wall. E_1, The cannula placed in the duct and retained by tying the traction sutures. A circular tie is placed just behind the flange of the cannula. E_2, The incision in the bowel is made to place the duct just outside the submucosa and lie in a short tunnel in the wall of the ileum. The purse-string suture is so placed in the submucosa as to close it snugly around the duct just behind the flange of the cannula. This manipulation should serve to exclude the pancreatic secretions from the anastomotic bed and bring the mucosal surfaces of bowel and duct into close apposition.

F, The completed operation and a detailed illustration of the path of the duct and cannula through the wall of the bowel.

resection of duodenum; resection of the head of the pancreas; resection of approximately eighteen inches of proximal jejunum; resection of biliary fistula, cholecystojejunostomy; section and ligation of common bile duct; transplantation of pancreatic duct into the jejunum, gastrojejunostomy (Fig. 5).

Procedure.—Through a transverse incision extending from the midline halfway between the xiphoid process and umbilicus and extending laterally to the right to include the biliary fistula, which was developed by dissection down to the gall bladder, this patient was explored. Immediately very dense adhesions were encountered, the division of which consumed considerable time. The common bile duct, approximately 3½ cm. in diameter, was identified. No masses could be palpated in the gall bladder or common duct down to the point where it entered the head of the pancreas. The tail and body of the pancreas appeared normal. The head of the pancreas was involved in a mass approximately 6 cm. in diameter.

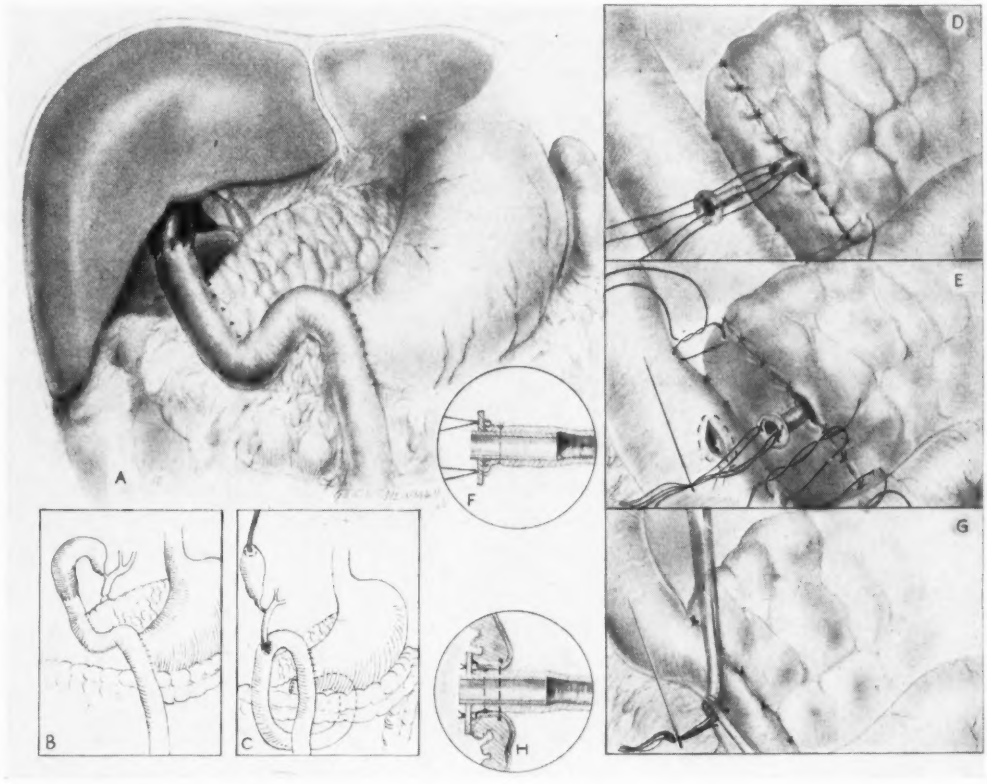

Fig. 5.—Resection of the head of the pancreas with reimplantation of the pancreatic duct.

A, The completed operation as performed on W. E. W.

B, The schematic illustration of *A*.

C, The schematic representation of a suitable procedure when only a portion of duodenum and no jejunum are excised. The pancreatic and biliary ducts are implanted into the jejunum and the gall bladder is drained during the immediate postoperative period.

D, Showing the capsule of the pancreatic stump closed and the silver cannula being placed in the duct.

E, The cannula is tied in place, the traction sutures are threaded onto a straight needle, the capsule of the pancreas is sutured to the jejunum posteriorly, and the purse-string suture has been laid down in the jejunum.

F, A detailed illustration of the cannula and duct in cross section.

G, The cannula and duct have been hauled into the anastomotic bed, the purse-string has been tied, the anterior edge of the capsule of the stump of pancreas has been sutured in place, and the bowel is being deformed by pressure with a clamp to allow the traction sutures to be cut short.

H, A detailed cross section of the cannula and duct as retained in the jejunal wall.

Pancreatic tissue overlying this mass, however, appeared normal. The mass was stony hard. A small lymph node of normal consistency was removed. A frozen section failed to show any evidence of metastasis to this gland. After mobilization of the duodenum and approaching the pancreas from behind, it was obvious that the head of the pancreas was involved in a carcinomatous growth, and resection was undertaken following the procedure outlined by Pearse.[10] The stomach was resected 10 cm. proximal to the pylorus. The duodenum was then developed and approximately one-third of the pancreas was resected. In resecting the pancreas, its capsule was incised and the lobules of pancreas were separated by blunt dissection. Vessels were clamped and tied with fine black silk. In this manner, it was possible to identify the pancreatic duct, and it was developed for a distance of about 1 cm. After double ligation, the duct was divided. The silk suture on the pancreatic duct was left long for subsequent identification. The common bile duct was closely adherent to the pancreas and was approximately 1½ cm. in diameter at this point. The common bile duct was clamped, divided, and triply ligated with No. 1 braided black silk. These ligatures were carefully placed with a graded amount of pressure from the proximal to the distal tie with the hope that they would not cut through with resulting biliary drainage, because it did not appear feasible in this instance to anastomose the common bile duct with the bowel. Remaining very close to the duodenum in order not to damage the superior mesenteric vessels, its dissection and development was continued down beyond Treitz's ligament. The defect in the transverse mesocolon was closed after the duodenum and resected portion of the stomach had been brought down through the opening. Approximately eighteen inches of jejunum were resected in order that the distal jejunal segment could be brought anterior to the transverse colon and sutured to the end of the gall bladder.

The pancreatic duct was then implanted into the jejunum. Holding the pancreatic duct over the index finger, it was divided through one-half of its diameter. Two fine arterial traction sutures of 5-0 Deknatel silk armed with a needle on each end were placed in the opposite cut edges of the duct and these sutures were threaded through holes in the flange of a small silver cannula. The shaft of the cannula was then inserted into the duct with the aid of the traction sutures which were securely tied to retain the cannula in the pancreatic duct. These sutures were left long and were to be subsequently threaded onto a large-eyed needle to serve as traction sutures to haul the cannula and the pancreatic duct into the site selected for its implantation. A circular tie of fine black silk was placed around the pancreatic duct just behind the flange of the cannula. It was immediately evident that pancreatic secretions were flowing from the end of the cannula. The cut edges of the pancreas were now proximated with interrupted fine black silk sutures to within 1 cm. on either side of the pancreatic duct. The site for implantation of the duct into the jejunum was selected to avoid any tension between the gall bladder and pancreas. A purse-string suture of No. 000 braided Deknatel silk was placed in the jejunum on the antimesenteric border at the site selected for the implantation of the pancreatic duct. The capsule along the posterior edge of the pancreatic stump was sutured to the jejunum with interrupted fine black silk sutures. An opening was now made into the jejunum just large enough to admit the flange of the cannula. The traction sutures previously prepared and threaded onto a long straight needle were carried through the opening in the jejunum and out through the opposite wall of the bowel. Traction on these sutures served to draw the cannula and pancreatic duct into the site of anastomosis. The purse-string suture was now pulled up firmly and tied, retaining the pancreatic duct in its anastomotic bed. The anterior edge of the capsule of the pancreatic stump was now sutured to the jejunum with interrupted fine black silk, thereby bringing the pancreatic stump into close apposition with the jejunum. Gastrojejunostomy was performed, care being again taken that there be no tension between the pan-

creatic stump and the gastric anastomosis. After placing 5 Gm. of sulfathiazole powder, suspended in normal saline solution, in the peritoneal cavity, the abdomen was closed, a single Penrose drain having been placed so as to pass behind the anastomosis between the jejunum and gall bladder and extend up to the neighborhood of the common duct. Silk was used throughout this operation. The entire operative procedure consumed seven and one-half hours, during which time the patient received 500 c.c. of 10 per cent glucose in normal salt solution intravenously, followed by 500 c.c. of citrated, whole blood.

Pathologic Diagnosis.—Carcinoma arising from duct epithelium and infiltrating the adjoining wall of the duodenum and the pancreas. Tumor of low-grade malignancy. Hyperplastic lymphadenitis.

Postoperative Course.—The patient did unusually well. Wangensteen suction was applied for nine days, 200 Gm. of intravenous amigen daily for four days, then 100 Gm. daily for an additional five days, as well as 200 Gm. of intravenous glucose daily.

Temperature elevation averaged about 1° F. for nine days and then returned to normal.

A mild degree of jaundice continued for ten days postoperatively.

The position of the silver cannula was observed by x-ray daily. It disappeared from the site of anastomosis on the thirteenth postoperative day. Healing occurred per primam and the patient was allowed up twenty-one days after operation and dismissed ambulatory, Nov. 5, 1943.

At no time during the postoperative course was glycosuria observed. The blood sugar concentration was normal.

The stools contained no neutral fat, and aspirated gastric contents showed trypsin to be present by the technique of Schmidt.[11]*

The patient was well four months after operation.

DISCUSSION

The reimplantation of the pancreatic duct into the alimentary tract has been done for a considerable time, but the practice has been either experimental or an unusual incidental accomplishment which was considered of little real value until the recent importance assumed by surgery of the pancreas stimulated by the work of Whipple and his co-workers,[5] Brunschwig,[12] and a number of subsequent workers' reports.

It is interesting to note the change in attitude toward the importance of the preservation of the pancreas to avoid atrophy, especially of the islet cells.[13] Even if these changes could be tolerated by man, the practical importance of avoiding the troublesome postoperative development of pancreatic fistulas makes it highly desirable that a dependable procedure be established to secure drainage of the external secretions of the pancreas into the alimentary tract. This would serve not only to ensure a more normal digestion, but also to protect the gland against atrophic alternations involving the hormonal secretions.

In 1935, Whipple, Parsons, and Mullins made the following statement: "We can form no idea of the number of unpublished cases in which it (the reimplantation of the head of the pancreas or duct) has

*The observations on trypsin were made by Dr. H. H. Sweets of the Department of Pathology.

been tried and resulted fatally, but it has seemed to us, because of the digestive action of the pancreatic ferments, that the hazard of the operation is too great to be advocated." Whipple's re-evaluation, in 1943,[13] of the importance of the preservation of the pancreas after eight years additional intrinsic interest and experience in surgery of this gland is as follows:

> Because of the variable findings in both experimental animals and in man with the pancreatic juice excluded from the gastro-intestinal tract, it seemed to me that the technic of radical pancreaticoduodenectomy should be changed so as to re-establish the flow of pancreatic juice into the jejunum, in order to improve the existing impaired fat digestion of these patients in whom the flow of pancreatic juice had been blocked for varying intervals, and also to avoid the very annoying complication of a pancreatic fistula which so frequently follows the exclusion operation. The jejunum is considered preferable to stomach because of the neutralizing effect of gastric juice on pancreatic ferments.

In contradistinction to this view, Brunschwig[14] points out that evidence to date indicates that some patients absorb normal quantities of fat, have normal stools, and do well without pancreatic juice entering the gastrointestinal tract.

It is hoped that the technical procedure for the implantation of pancreatic ducts into the bowel described in this communication may remove the obstacle mentioned by Brunschwig (1943), quote: "The successful anatomic implantation of the pancreatic stump into bowel in man has not yet been demonstrated to afford normal or appreciable secretion of pancreatic juice into the bowel."

In comparison to the case presented earlier in this communication, the following abstract is given.

CASE ABSTRACT

E. A. H. (J. S. H. No. 78453), white man, aged 55 years, was first admitted to John Sealy Hospital Oct. 26, 1942, complaining of painless jaundice of three months' duration. Previous history was noncontributory. An enlarged distended gall bladder was palpable. There was roentgen evidence of mass pressing into duodenum.

Laboratory Data.—

Blood: Red blood cells, 3.66 millions; hemoglobin, 64 per cent; white blood cells, 10,500; 82 per cent polymorphonuclears; 13 per cent lymphocytes; 3 per cent monocytes; 2 per cent eosinophiles; Wassermann reaction negative; nonprotein nitrogen, 29.6; icteric index, 200; blood cholesterol, 550 mg. per cent; prothrombin time, 1 min. 45 sec.; control, 55 seconds.

Urine: Specific gravity, 1.011; reaction, alkaline; albumin, 1 plus; negative sugar; urobilin and urobilinogen negative.

Stools: No parasites; acholic; moderate amount of fat.

Diagnosis.—

Common duct obstruction; carcinoma of head of pancreas.

Operation.—Nov. 2, 1942, operation was performed using the procedure of Herman Pearse,[10] partial gastric resection, resection of head of pancreas, ligation of

pancreatic duct (exclusion), ligation of common duct, resection of duodenum, resection twenty inches proximal to the jejunum, cholecystojejunostomy, gastrojejunostomy. Silk was used throughout.

Pathologic Diagnosis.—Adenocarcinoma of the pancreas.

Postoperative Course.—The patient did well until the third postoperative day, when he complained of sudden epigastric pain and temperature rose to 104° F.; on the following day pancreatic drainage from the wound was evident. Pancreatic secretions collected quantitatively for a period of five months and varied from 500 to 1,500 c.c. daily.

The carbon dioxide combining power was 30 to 40 volumes per cent.

Although this patient lived for five months and took food quite well until the last month of life, he did poorly, was dehydrated, failed to gain weight, and continued bedridden. There was no diarrhea or fatty stools. Stools were brown and jaundice cleared promptly following operation. For the last month of survival, the patient had abdominal cramps with moderate distention and occasional vomiting. Gastrointestinal series did not show evidence of obstruction. March 10, 1943, five months and eight days after operation, the patient died shortly following pulmonary embolism. Autopsy was not permitted.

In this instance there was no apparent difficulty regarding fat digestion, but the loss of fluids and alkalies in the pancreatic secretions undoubtedly contributed greatly to this patient's unsatisfactory convalescence.

The manner of pancreatic duct stoma obtained following reimplantation will, no doubt, depend to a degree on the type of healing secured. One should expect a poor result following the rather difficult procedure outlined by Coffey[15] in his experimental implantation of the entire stump of the pancreas into the gastrointestinal tract. Placing the end of the pancreas into such an abnormal environment will undoubtedly result in extensive scarring and induration about the outlet. The very simple technical procedure described by Cattell[16] is readily performed, but it carries with it the danger of immediate leakage of digestive ferments between the stump of the gland and the raw bed made in the wall of the bowel before the necrosing suture cuts through the submucosa of the bowel, which might on occasion result in extensive degeneration of tissue with necrosis and much scar formation at the immediate site where primary healing is desired. Just how much damage will result to the pancreas from reflux of bowel contents into its duct system is problematical. It would seem desirable, however, to obtain the best possible union of the duct and bowel, with preservation of normal bowel mucosa immediately surrounding the stoma, and it is felt that the procedure described in detail in this communication will, since the digestive ferments are diverted away from the healing bed, give a suitable stoma without imposing a too difficult and timeconsuming techincal procedure. In fact, the introduction of the small cannula and the implantation of the duct is relatively easily accomplished. In 1917 Patrie and Vale[17] described an experimental procedure by which the pancreatic duct was transplanted into various levels of the bowel.

Since the pancreatic duct has such a pronounced tendency to reanastomose with the bowel of the dog, it is suggested that this same event might occur in the human being, especially where the stump of the excluded pancreas lay near the line of suture between stomach and jejunum. It is suggested, therefore, that the gastric and jejunal contents be studied for trypsin to ascertain if such spontaneous anastomoses or internal fistulas have occurred in some of the patients following the exclusion operation of resection of the head of the pancreas.

SUMMARY

An experimental method for the implantation of biliary and pancreatic ducts into the gastrointestinal tract is presented in detail with a description of the tendency shown for spontaneous reanastomosis of pancreatic ducts and bowel in dogs.

A detailed description of the successful application of this procedure to man is given, and the importance of protecting the pancreas from atrophy is discussed. It is concluded that a procedure ensuring the successful re-establishment of drainage from the external pancreatic secretion with the alimentary tract and prevention of pancreatic fistulas is a required part of partial resections of the pancreas.

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THE SURGICAL MANAGEMENT OF DUODENAL DIVERTICULA

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SEVERAL years ago I saw a patient in whom another surgeon had excised the common bile duct while removing a diverticulum of the second part of the duodenum. This made such an impression that the literature was studied in an effort to find out how such an accident might be avoided. No completely satisfactory method was found so a procedure was planned that appeared to give assurance of safety to the ducts. Recently an opportunity was offered to test this and it worked so well that it is reported.

Fletcher and Castelden[9] describe primary duodenal diverticula as follows: "They never arise in the first portion, are seen occasionally in the third and fourth portions but in the large majority of instances (75 per cent) are found springing from the concave inner aspect of the descending limb, never far from the ampulla of Vater, and lying in close relationship to the head of the pancreas." They have an incidence of from 0.16 to 3.8 per cent in different reports[7, 25, 26, 28] of x-ray and post-mortem examinations. In Morton's[23] review of the cases operated upon, 65 per cent of the single, primary diverticula were in the second part of the duodenum where danger to the ducts is involved.

INDICATIONS FOR OPERATION

There is much discussion in the literature about the need of operation in primary duodenal diverticula. Certainly most of them do no harm and should be left alone. A few (5 per cent in our series) cause definite symptoms which require surgical intervention. Morton[23] says that "There is justification for surgery of duodenal diverticula upon the following grounds":

A. Mechanical
   1. Symptoms from stasis in the diverticulum
   2. Symptoms from obstruction of the biliary tract, pancreas, or duodenum

B. Inflammatory
   1. Primary diverticulitis or perforation
   2. Secondary inflammation of the biliary tract, pancreas, duodenum, or retroperitoneal tissues

C. Neoplastic change

There is no question of the need for surgery if inflammation in the diverticulum causes gangrene, perforation, or peritonitis as in the cases

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of Boland,[4] Beaver,[3] Monsarrat,[20] and others. Nor is there hesitation if tumor develops, such as is recorded by Mendillo and Koufman[19] or Morrison and Feldman.[22] But debate or disagreement occurs when the diverticulum is causing symptoms from stasis alone. It is improbable that it can cause trouble if it empties easily and drains well. Therefore, the first information desired is whether or not x-ray study shows barium trapped in it. If barium is retained and especially if localized tenderness is present at this time, then it may be suspected as the cause of the symptoms. If there is stasis in the diverticulum and associated

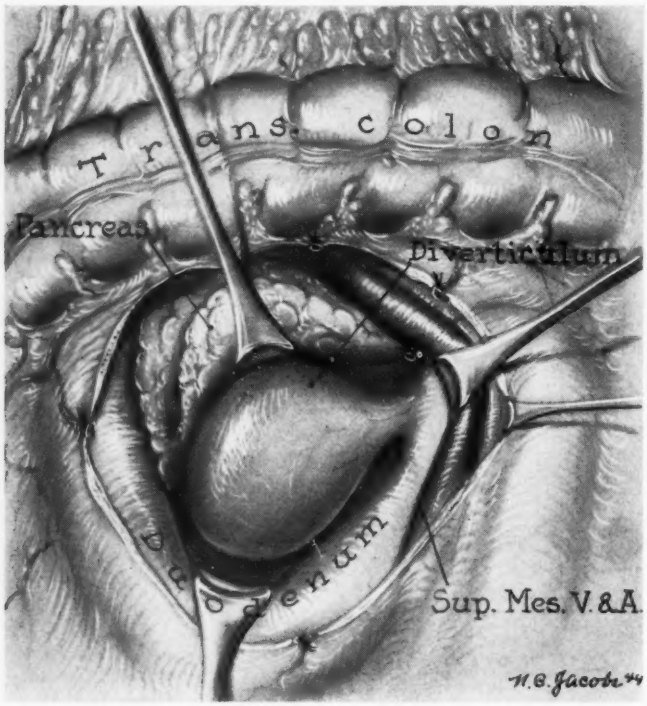

Fig. 1.—The best exposure of a diverticulum of the third part of the duodenum is usually obtained by dividing the mesocolon, retracting the superior mesenteric vessels, and elevating the pancreas. The approach through the gastrocolic omentum was also found to be satisfactory in one of our cases (R. D. No. 104466).

inflammation of the biliary tract or pancreas, the diverticulum may be responsible. A more difficult question is whether stasis in a duodenal diverticulum may cause symptoms in the presence of gallstones. McQuay[18] reports a case in which a calculous gall bladder was removed without excising the diverticulum in which relief was not obtained. Lucinian's[15] patient, who had a cholecystectomy for stones, "was relieved from pain and distress for a short period after operation but these returned, identical in intensity and character." She was cured by excision of the duodenal diverticulum. From these cases and from theoretical considerations, it seems desirable to excise at the time of cholecystectomy a peri-Vaterian diverticulum which is the site of stasis.

OPERATIVE MANAGEMENT

If operation is decided upon, what is the best method of attack? In some instances the indirect approach by gastroenterostomy has been made. This is probably justifiable only with multiple diverticula which cannot be removed. Guthrie and Brown[11] and McQuay[18] report cases in which gastroenterostomy was done previously without relief and in which the authors cured the condition by disconnecting the anastomosis and excising the diverticulum. On the whole, gastroenterostomy appears to evade the issue.

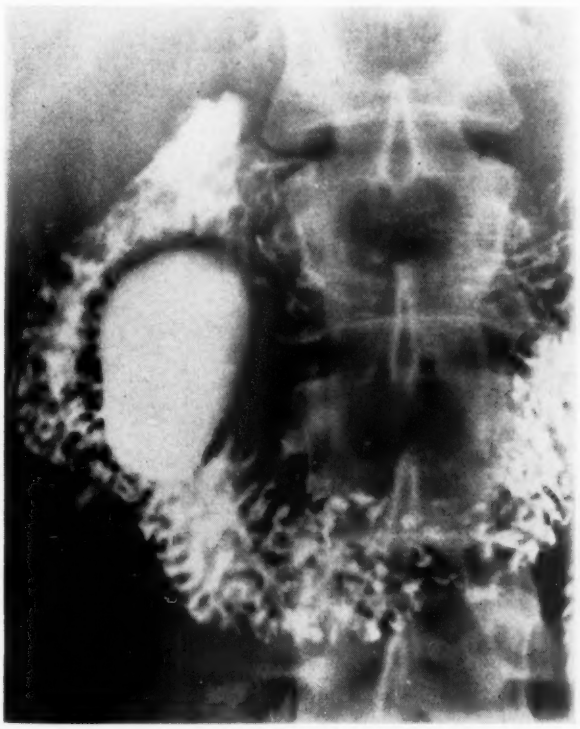

Fig. 2.—This diverticulum of the second part of the duodenum is in the typical location on the concave side of the loop. It was tender, retained barium, and showed signs of inflammation on pathologic examination.

The excision of diverticula of the third or fourth parts of the duodenum presents no particular problem except adequate exposure. The first operation reported in this country by Basch[2] was done by dividing the mesocolon. Later Maclean[17] and others have used this approach. The superior mesenteric vessels are retracted to the left and the pancreas elevated as shown in Fig. 1. Diverticula of this part of the duodenum may also be exposed by dividing the gastrocolic omentum and approaching them through the lesser omental sac.

Diverticula of the second part of the duodenum are the commonest to require operation, yet are the hardest to remove safely. They are hidden in a retroperitoneal location behind the pancreas and medial to the duodenum (Fig. 2). Some surgeons have dissected through the

pancreas or have separated the pancreas from the duodenum, both of which paths may give bleeding and the possibility of pancreatic leakage. Maclean[17] describes a method of opening the duodenum, inserting a finger into the diverticulum and cutting down onto it through the pancreas. The most commonly used approach is by mobilization of the duodenum medially and rolling the diverticulum out from behind it. This is an avascular and a traumatic method which is very satisfactory but after this is done the hazards of the operation have just begun. Yet in the literature this usually ends the description and the words, "sac excised," "stalk ligated, divided, and inverted," are used to describe what is done to complete the operation. The dissection of tissue off the neck of the sac or its excision may injure the pancreaticoduodenal vessels, the pancreatic duct, or the common bile duct. Also the closure of the duodenum may damage or obstruct these structures. So it appears that these steps in the operation are the ones that most deserve study and they are the ones emphasized in the procedure described.

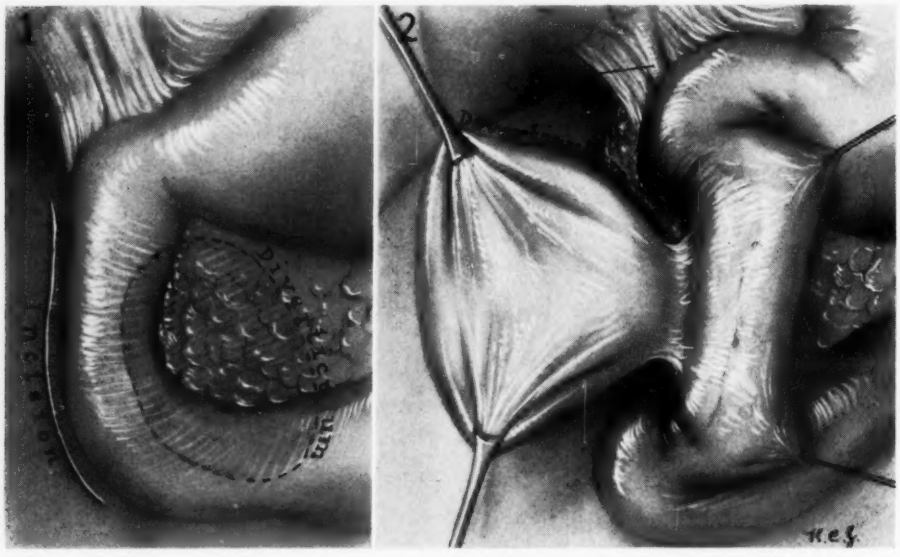

Fig. 3.—*1.* Shows the incision in the posterior peritoneum to the right of the duodenum used for mobilizing the loop to the left. The location of the diverticulum behind the pancreas is indicated.

2. The duodenum is held by stay sutures after it is rotated medially. The diverticulum has been freed by gentle traction and dissection and is held up on the right side of the bowel.

TECHNIQUE OF OPERATION

The abdomen is opened through a right rectus incision. The posterior peritoneum to the right of the duodenum is incised as is shown in Fig. 3, *1*, and the duodenum mobilized to the left. This peritoneal incision may be lengthened to allow complete rotation of the duodenum

if desired (restoration of embryologic position). Stay sutures are placed at the top and bottom of the loop and as it is rotated the wall of the diverticulum is presented. This is picked up and by means of gentle traction combined with dissection the diverticulum is drawn out to the right of the duodenum (Fig. 3 *2*). There may be attachments of thick tissue at the neck of the sac which are best left alone until later. The outer part of the sac is thin walled, therefore it can be inspected easily and then cut down the middle to within about one-half inch of the duodenal wall with safety (Fig. 4). If there is any doubt of this, transillumination can be used to look for any thickening

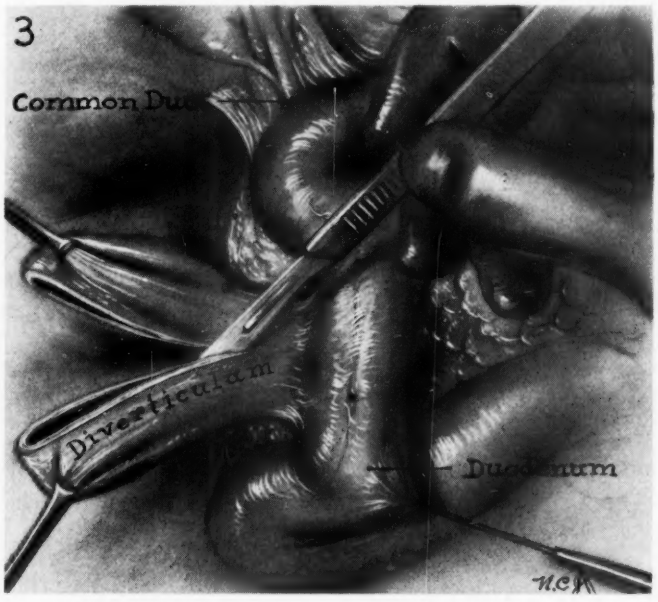

Fig. 4.—The diverticulum is slit open down its center to within about one-half inch of the duodenum. This allows transillumination or direct palpation of the neck of the sac before it is freed of surrounding structures. Duct injury is avoided by this precaution.

in the sac. Now one can look into the duodenum and try to locate the opening of the ampulla of Vater if desired. Whether or not it is seen, it is now safe to free the neck of the sac from the adjacent structures for the surgeon can transilluminate the wall, look on the inside and outside of the wall as he works, or put a finger in the neck of the sac and feel its thickness. After freeing the neck of the sac the same methods are used in cutting across it (Fig. 5). This cut can be made with confidence that no injury will be done when these precautions are taken. It should be remembered that because of the rotation of the duodenum the pancreaticoduodenal vessels are now behind the neck of the sac and the opening of the ducts are transposed.

The line of excision is placed about one-half inch from the duodenal wall leaving a cuff of tissue for easier closure of the defect as is done

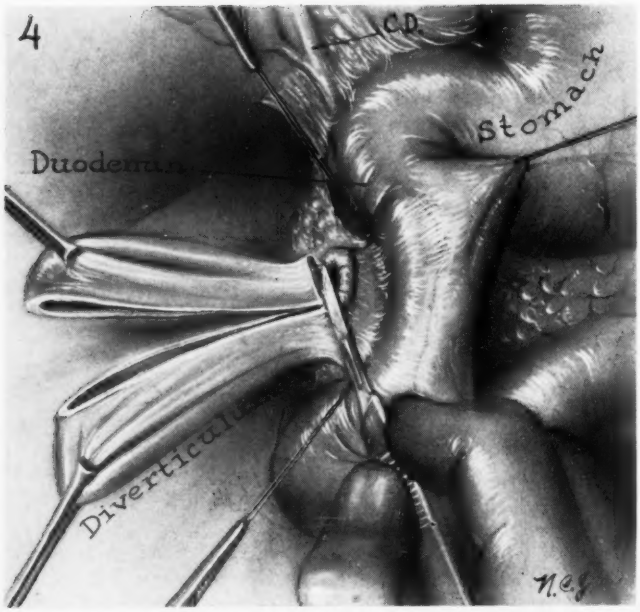

Fig. 5.—The greatest danger of duct or vessel injury comes with excision of the sac. If the surgeon has palpated the wall with a finger in the lumen or transilluminated the tissues, he can make the cut with confidence. A cuff of tissue is left as in esophageal diverticula to allow closure without narrowing the lumen of the bowel or catching the ducts in a stitch.

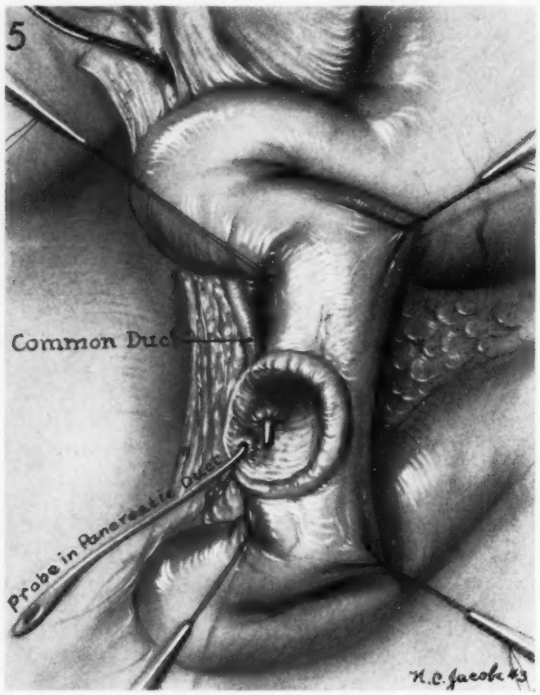

Fig. 6.—The view looking into the duodenum with the diverticulum excised. The rotation of the duodenum brings the pancreatic duct to the left where the opening is practically at the junction of the sac and the duodenal wall. In this case the opening of the common bile duct could not be readily located therefore the duct was opened above and a catheter passed down it. These probes are left in the ducts while placing the first row of sutures.

in esophageal diverticula. This also gives greater protection against duct injury for in some cases the ducts enter at the neck of the sac or at the junction of sac and duodenal wall. Through the opening produced one has a clear view of the duodenum and can now place a probe in the pancreatic and common bile ducts (Fig. 6). If the ampulla of Vater cannot be located, it is best to open the common bile duct above and pass a catheter down into the duodenum. It is urged that, unless the ampulla is well away from the margin to be closed, these probes be left in place until sutures closing the defect are placed. Before tying the stitches at the end of the opening one can take one last look at the ducts, verify that they have not been caught in a stitch, and then remove the probes. This gives a comforting assurance of an uncomplicated result. The details of closure of the duodenal wall and restoration of the duodenum to its normal position are shown in Fig. 7.

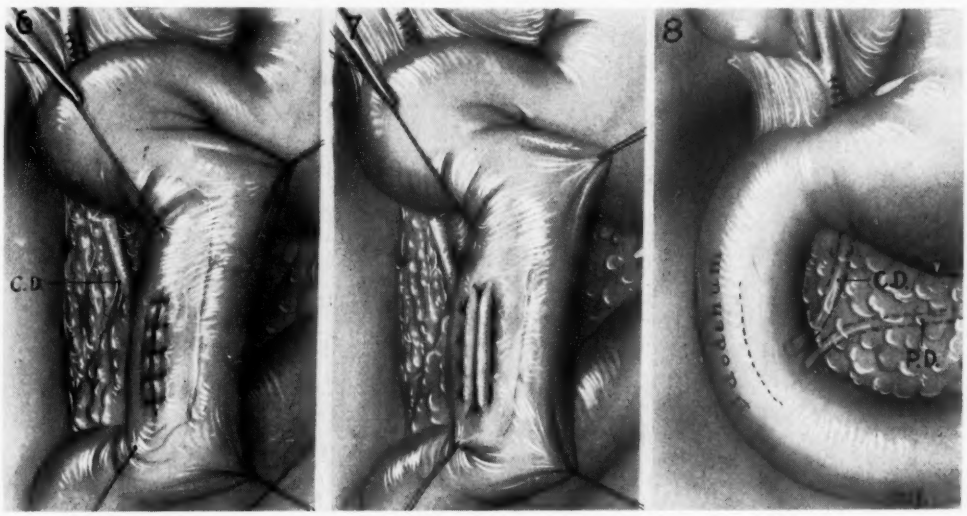

Fig. 7.—*6*, The first row of sutures is completed and the common duct is closed. Before tying the last stitches a final inspection is made and the probes removed from the ducts. *7*, The closure is completed. *8*, The duodenal loop is replaced to complete the operation.

SUMMARY

Only a small number (about 5 per cent) of duodenal diverticula require operation, but the majority of these are in the second part of the duodenum where removal endangers the pancreatic and common bile ducts and the pancreaticoduodenal vessels. The hazardous part of removing these peri-Vaterian diverticula comes with dissecting free and dividing the neck of the sac and closing the defect in the duodenal wall, for it is here that the duct or vessel injury occurs. An operation is presented that is designed to avoid these dangers.

My surgical chief, Dr. John J. Morton, is also interested in this subject and I am indebted to him for information received, not only from his excellent review but also from personal conversation.

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TREATMENT OF LARGE BOWEL OBSTRUCTION

Transverse Colostomy—Incidence of Incompetency of Ileocecal Valve; Experience at the University of Minnesota Hospitals

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ALTHOUGH there has been a marked drop in the mortality of patients with acute small bowel obstruction in recent years,[8, 17] a review of the literature does not show such generally gratifying observations in acute obstruction of the colon,[1, 4, 14] and only a few reports, such as that of Gregg and Dixon, show figures (13.6 per cent) better than those on the small bowel lesions. In view of this fact, a brief review of some of the factors involved and of the practices and results at the University of Minnesota Hospitals seems in order. This report is intended to serve as a complement to a previous communication on small bowel obstruction,[8] and certain features discussed more fully there will be only mentioned here.

INCIDENCE OF COLIC OBSTRUCTION

The bulk of the articles on large bowel obstruction is limited to discussions of carcinomatous strictures, the commonest cause of obstruction in this viscus. The frequency of colic obstructions, aside from this connection, is, therefore, difficult to establish. The frequency of acute complete colic obstruction in carcinoma of the colon is variously estimated in published reports. Campbell estimates it at more than 30 per cent, Burgess at 35.6 per cent, and Graham at 16 per cent, while Gregg and Dixon report the Mayo Clinic figure at only 5.6 per cent of 2,730 cases, a figure possibly reflecting a different type of surgical practice.

In the Mayo Clinic figures, two-thirds of the colic cancers causing obstruction were in the descending, sigmoid, or rectosigmoid colon, while only one in seven lay cephalad to the splenic flexure, findings largely explicable on the basis of the more solid character of the fecal matter and smaller diameter of the left colon.[30]

Acute obstruction on other bases is less common, but extracolic malignancies and pelvic and sigmoid inflammatory lesions rank next in importance, and volvulus of the sigmoid is a poor third in this

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country, although it is apparently much more common in some European countries.[30]

Partial obstruction is much more common, but it is not easy to evaluate statistically because of the difficulty in establishing sharp lines of demarcation between nonobstructing and minimally obstructing lesions. The present report is concerned with acute complete colic obstruction only.

PHYSIOLOGIC CHANGES IN ACUTE COLIC OBSTRUCTIONS

The physiologic changes occurring in obstruction of the colon differ only in certain respects from those outlined previously for small bowel obstruction, and will be discussed here only in those respects.

The low position of the obstructing lesion in the intestinal tract usually allows absorption by the bowel above that point of much of the food, water, and salt taken by mouth. These patients, therefore, like those with terminal ileac obstruction, are regularly free from the hypochloremia, uremia, and marked dehydration seen in obstructions high in the small intestine.

A factor further tending to inhibit chemical imbalance is the frequent absence of significant vomiting, a point commonly attributed to competency of the ileocecal valve.[25, 29, 30] Using an intracolic pressure of 50 mm. of Hg, Sperling found the ileocecal valve competent to prevent reflux into the ileum in five out of fourteen patients studied with barium enema and the fluoroscope. Sperling and others have reported series of cases in which perforation of the cecum had occurred without distention of the terminal ileum, and he stresses the importance of the ileocecal valve in rendering colic occlusion a type of "closed loop" obstruction.[18] Since it is in the cecum that the colic wall is thinnest and the diameter is greatest, ischemic necrosis and perforation usually occur at this point in unrelieved cases.[6, 26, 30] Perforation also can occur at this point in cases with incompetent ileocecal valves (see Comment).

Early in left colic obstruction, distention may occur primarily just proximal to the lesion, and, since peristaltic rushes are far less frequent here than in the ileum, cramps and borborygmi may be present at intervals of from ten to thirty minutes or longer. Later the entire proximal colon usually becomes distended, and cramps and borborygmi then are apparent as each peristaltic wave in the ileum forces more material into the already distended cecum (or into the distended lower ileum if the valve has proved incompetent); the interval between cramps now is from three to ten minutes, the interval between major contraction waves in the ileum. It may be shorter if distention extends higher in the small bowel, or, later in the process, cramps may be absent altogether.

DIAGNOSIS OF COLIC OBSTRUCTION

In carcinomatous colic obstruction, "almost invariably a history of constipation extending over some period of time is obtained; there frequently have been attacks of abdominal pain associated with temporary meteorism, during which time the expulsion, of gas and feces, has been accomplished with extreme difficulty or not at all. The observation of blood and mucus in small quantities in the stool has, at times, been previously noticed; alternating periods of constipation and diarrhea may be complained of. Anschütz states that in his series, fourteen came with acute intestinal obstruction, as the first evidence of the disease. When such a patient presents himself for examination, the abdomen is frequently distended and occasionally the patterns of the colon may be seen in the form of a horseshoe-shaped swelling around the periphery of the abdomen.

"Vomiting is not infrequently absent altogether, despite enormous distention. Occasionally, vomiting may be present initially. The duodenal tube may reveal that gastric retention is absent. These significant findings owe their occurrence to the action of the ileocecal valve and sphincter and are of great value in helping to determine the exact nature of the obstruction present. A patient with occlusion of the colon may not appear particularly ill; yet, it is one of the most vicious obstructions observed clinically.

"Digital examination of the rectum frequently shows this cavity to be empty. Bimanual palpation aided with one hand over the abdomen occasionally renders a mass palpable which could not be felt by abdominal palpation or rectal examination alone. The abdomen, though tympanitic, is moderately soft and not tender; when tenderness is present it is usually found over the cecum—a warning that the viability of the bowel is threatened by the enormous distention."[30]

Intestinal colic is present at some time in each case, but may be absent when the patient comes for relief. Gas pains early in the phase of complete obstruction usually come at intervals longer than ten minutes, but later, when the cecum or even the terminal ileum is also distended, they may come at the more frequent intervals of small bowel colic, although they may now be absent altogether.

Scout films of the abdomen regularly show distention of the colon from the cecum to the point of obstruction, which cannot infrequently be localized in this manner (Fig. 1).[28] Gas, due to stasis, may be visualized in the terminal ileum frequently, and distention of the small bowel may occasionally be present. Barium enema roentgen examination may fail to reveal the obstruction site, allowing the contrast medium to pass relatively freely in the cephalad direction, and it may, in addition, culminate in rendering complete an obstruction which has been partial until that time.

Differentiation among the various causes of colic obstruction may be impossible until pathologic examination, but unless the distention is extremely marked, accurate diagnosis is usually possible at operation, whether the lesion is carcinoma, diverticulitis, or compression or infiltration from outside the bowel. Differentiation from small bowel

obstruction is facilitated by the almost constant presence of vomiting, often of fecal character, in that condition, by consistent presence of cramps at intervals less than ten minutes in small bowel obstruction, and by the ladderlike arrangement of loops of small bowel usually apparent on the scout film. Infrequently, colic obstruction, especially if situated in the right colon, may simulate small bowel obstruction in regard to all of these features. Under such circumstances the situation of the patient may be precarious because of failure to recognize the danger of perforation of the cecum.

Fig. 1.—Roentgen picture of abdomen of a patient with complete obstruction in the pelvic colon. In this case the ileocecal valve has prevented regurgitation into the ileum, and true "closed loop" obstruction is present. (From Wangensteen, O. H.: Intestinal Obstructions, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, p. 39.)

Preoperative diagnosis of volvulus of the sigmoid colon is of great practical importance, for it is fundamentally a greater threat to the blood supply of the sigmoid loop than simple obstruction is to that of the cecum, and a left lower rectus incision must be made to deal with it adequately. There is usually a lifelong story of constipation, and the condition is particularly prone to occur in patients with megacolon, in whom the sigmoid loop is abnormally large and long.[32] There

is likely to be a history of previous attacks and, at the time, a story of sudden onset of abdominal pain with increasing distention and failure to pass flatus. Distention quickly becomes marked, and abdominal tenderness and rebound tenderness with leucocytosis are likely to appear. Roentgen pictures usually show a single loop far more enlarged than others, with a tendency to extend up to the right upper quadrant and even, at times, to overlie the liver. Upright pictures usually show considerable amounts of fluid in such a loop, and cautious barium enema examination, which is permissible here, may reveal clearly the area of twist and distortion at the base of the mesosigmoid (Fig. 2).

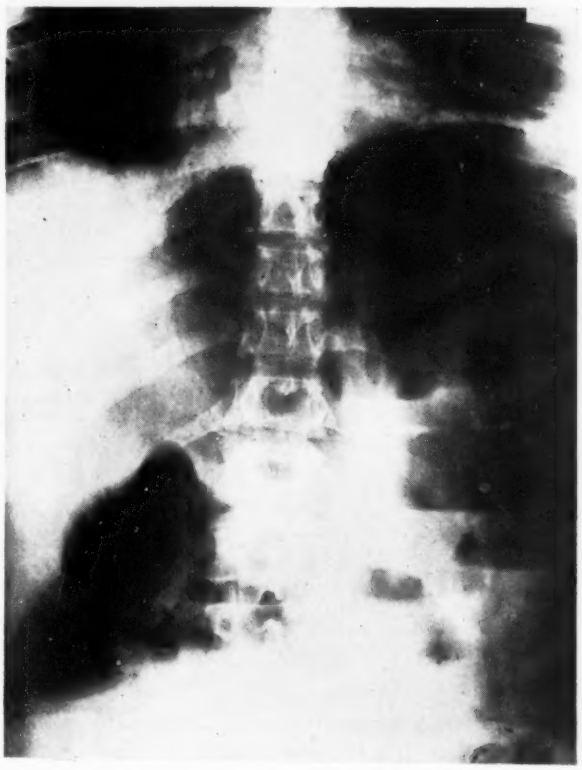

Fig. 2A.—Volvulus of the sigmoid colon. Upright picture of the abdomen, showing extension of the greatly enlarged sigmoid loop to the upper limits of the abdomen. Note fluid levels. The transverse colon and cecum are also distended, but the ileum is not seen.

TREATMENT OF COLIC OBSTRUCTIONS

Simple Obstructions.—Although the possibility of primary surgery upon the obstructing lesions appeals to the imagination, experience has shown that the risk is more than twice as great as that of preliminary decompression followed by resection after recovery from distention.[13, 16, 30] These results are considered due to edema and poor circulation in the thinned and stretched bowel wall, combined with actual

bacterial invasion from the lumen. Only after these changes have been corrected by recovery after decompression has surgery to the lesion itself proved feasible.

Decompression of the distended colon seen in acute obstruction is to be regarded as a surgical emergency, for a large number become "closed loop" obstructions without possibility of relief by regurgitation, and the greatly increased tension constricts the blood vessels of the bowel wall, especially in the cecum, thus to all practical purposes

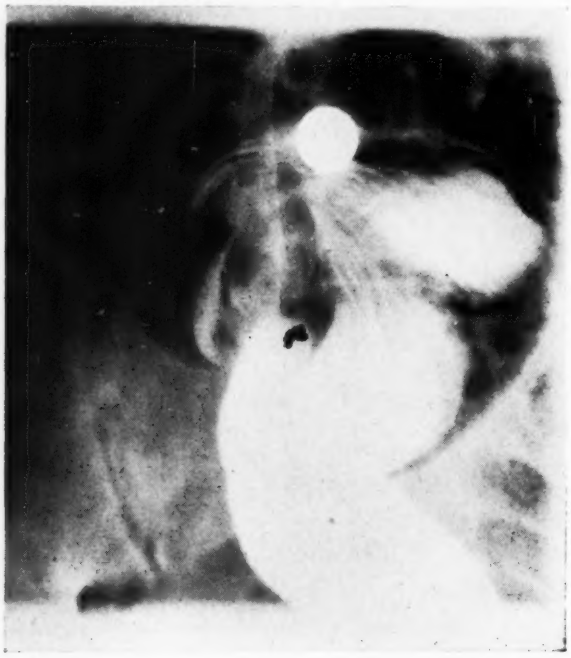

Fig. 2*B*.—Volvulus of the sigmoid colon. Detail picture of the left lower quadrant of the same patient upon administration of a small barium enema, showing clearly the site of twist. Barium also appeared quickly in the right upper quadrant loop.

converting the obstruction from a simple to a strangulating one, with the imminent threat of cecal perforation hanging over the patient.[6, 18, 25] Cecal perforation has even been observed to occur in one case of acute colic obstruction with an incompetent ileocecal valve and distention of the ileum; a few other patients have been treated for small bowel obstructions in the presence of small bowel distention and incompetent ileocecal valves under the erroneous impression that small bowel obstruction was responsible for that distention, and in none of this group has perforation of the cecum occurred.

Among most surgeons, cecostomy has long been considered the procedure of choice for decompression of the distended colon.[13, 33, 34] Because of the impossibility of *aseptic* decompression in doing cecostomy and the difficulty of complete delivery of the cecum in the presence of

marked distention, the mortality is high; Wangensteen[30] states that the mortality of this procedure at the University of Minnesota Hospitals was nearly 50 per cent, a figure corroborated by Campbell and others.*

Several years ago, Wangensteen suggested that decompression in acute left colic obstruction be accomplished by transverse colostomy. He emphasized that the incision could be precisely placed over the distended transverse colon to be exteriorized if a preliminary scout film with a coin on the umbilicus was made (Fig. 3). This is a sound precautionary measure, although I have not seen a case in which it has

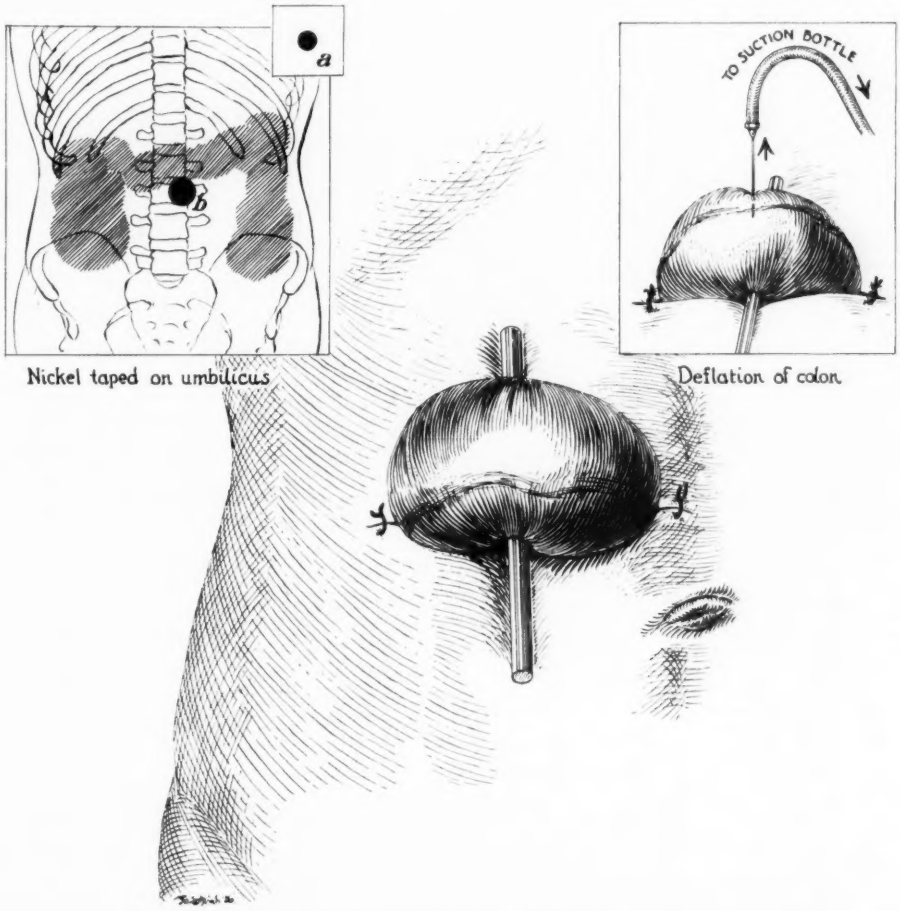

Fig. 3.—Technique of decompressing the distended colon. Sketch of a radiogram from a case. A five-cent piece is taped over the umbilicus. In the insert, on the left, the actual size of the nickel drawn to scale is shown in *a*. The 33 per cent enlargement on the anterior abdominal wall is shown in *b*. The intestinal coils within the abdomen are enlarged 25 per cent. In the insert on the right, the method of deflating the colon on completion of the operation is shown. After a few such aspirations, the bowel is incised and a tube is inserted before it is finally cut across. The tension in the bowel is determined before its contents are aspirated. (From Wangensteen, O. H., Intestinal Obstructions, ed. 2, Springfield, Ill. Charles C Thomas, Publisher, p. 179.)

*In a paper which appeared after this article was submitted, Coller and Ransom report losing five of seven patients in whom cecostomy was done in the presence of high-grade obstruction. (Coller, F. A., and Ransom, H. K.: Carcinoma of the Rectum. Conclusions based on Twelve Years' Experience With Combined Abdominoperineal Resection, Surg., Gynec. & Obst. **78**: 304, 1944.)

led to alteration in the already planned incision. Wangensteen particularly emphasized in his teaching at the clinic here that this procedure must be done through a transverse incision, preferably cutting across the right rectus muscle halfway between the umbilicus and the xyphoid. Patients have been referred to this hospital after attempts to accomplish decompression of the transverse colon through vertical abdominal incisions, and this procedure has failed because of inability to deliver the distended transverse colon through such an incision. Decompression of the bowel intraperitoneally in order to facilitate delivery through a vertical incision invites the hazards of cecostomy. Such decompression prior to delivery is almost never necessary after entry through a properly placed transverse incision.

In performing transverse colostomy, the colon is elevated over a glass rod and further fixed by fine silk sutures securing the omentum and fatty tags to the peritoneum and rectus sheath. In the presence of distention, no sutures are placed in the bowel wall proper. A little sulfanilamide or sulfathiazole powder is dusted along the suture line, and massive petrolatum dressings are placed to cover all the field but a small area of the bowel before insertion of a hypodermic needle for determination of intraluminal tension, and decompression. If the bowel refills quickly, it is aspirated every few hours during the next three days; at that time the anterior half is cut with the cautery, and at seven or eight days after operation the bowel is cut down to the glass rod. This procedure accomplishes complete deviation of the fecal stream, a matter of some importance in subsequent surgical procedures.[5, 10, 30]

In those occasional instances in which the lesion has been palpable on rectal examination and in which the distention has not been too extreme, decompression has been accomplished by left inguinal sigmoid colostomy. Such procedure is open to the objection that the sigmoid colon may not be found free enough for delivery without dissection in the presence of distention, but it offers the hope of simplification of subsequent operative management.

In one or two instances here decompression has been undertaken by passage of a rectal tube past a low-lying rectal lesion. It is probably not to be recommended unless the lesion is very low.

When the lesion lies in the right colon, insertion of a catheter into the cecum by way of the appendix or the terminal ileum (with double-barreled ileostomy) must be performed, reserving cecostomy for only the rarest occasions.

The management of obstruction due to diverticulitis is essentially the same as that due to cancer and needs no special mention.

Volvulus of the sigmoid colon is potentially or actually a strangulating obstruction and, as such, demands immediate detorsion as well as decompression of the colon proximally. Many surgeons accomplish

both purposes by simple detorsion of the sigmoid loop, but Finsterer found thirteen recurrences in forty-seven cases, and this experience has been adequately corroborated. The risk of resection approaches 50 per cent in the experience of most authors,[14, 30] but six of Muschkatin's[20] seven patients survived after resection and use of extraperitonealized primary open anastomosis. The policy at this hospital has, nevertheless, been to exteriorize the sigmoid loop after detorsion. Preliminary placement of a rectal tube, as suggested by Hinton and Steiner, is helpful in emptying the distended sigmoid.

EXPERIENCE WITH COLIC OBSTRUCTION AT THE UNIVERSITY OF MINNESOTA HOSPITALS

In the six years from Jan. 1, 1938, to Jan. 1, 1944, fifty-three cases of acute complete colic obstruction passed through the General Surgical Operating Rooms at the University of Minnesota Hospitals. One additional patient, with volvulus of the sigmoid colon with perforation, arrived in moribund condition and died without surgery. This case is included in the study. During this same period the average yearly number of admissions for acute small bowel obstruction was thirty, so our incidence of complete colic obstruction is about one-third that of small bowel occlusion.

Specifically omitted from the present discussion are five additional cases, three of colitis (two ulcerative and one phlegmonous) and two of ileus secondary to other lesions; all five patients died without evidence of organic obstruction.

CARCINOMATOUS OBSTRUCTION OF THE COLON

Incidence of Obstruction in Colic Cancer.—In this series of fifty-four cases, carcinoma of the colon or rectum was the agent most frequently responsible for obstruction. There were thirty-five such cases. Inasmuch as a total of 367 patients with carcinoma of the colon passed through the general surgical operating rooms during this six years, the incidence of complete obstruction in colon cancer was 9.54 per cent. There were many other instances in which obstruction was partial or questionably present; they are not the subject of this review. Many of these 367 patients had carcinoma of the rectum. Some had colostomy only as a palliative procedure.

Sites of Obstruction in Colic Cancer.—Twenty-eight of the thirty-five patients had obstruction of the left colon. Six of the obstructions to the right colon lay at the hepatic flexure, although the primary lesion in one lay in the cecum, and obstruction was related to hepatic metastasis. One lay in the transverse colon, involving also the ileum. In the left colon nineteen of the twenty-eight patients suffered obstruction in the sigmoid loop and the remainder were almost evenly distributed among rectum, descending colon, and flexure (Table I).

TABLE I

SITES OF CARCINOMAS CAUSING COLIC OBSTRUCTION

SITE OF LESION	NO. OF CASES	MANAGEMENT		OBSTRUCTION DEATHS	
		TYPE	NO.	NO.	%
Rectum	4	Transverse colostomy	2	0	0
		Inguinal colostomy	2	0	0
Sigmoid colon	19	Transverse colostomy	18	1[1]	5.5
		Other[2]	1	1	100
Descending colon	3	Transverse colostomy	3	1[3]	33
Splenic flexure	2	Transverse colostomy	2	0	0
Transverse colon	1	Other[4]	1	0	0
Right colon	6	Variety	6	2[5]	33
Total	35			5	14.3
Transverse colostomy mortality				8%	

[1]The cecum was perforated at the time of surgery.

[2]A lesion of the sigmoid was exteriorized—peritonitis (see below).

[3]The lesion had perforated before surgery—liver abscesses and metastases and peritonitis.

[4]Miller-Abbott decompression[19] followed by Rankin[21] excision of lesion and resection of involved segment of ileum with primary anastomosis.

[5]One died a month later, while still in the hospital, of massive metastases to liver. One died of unknown cause at four days, massive ascites found at surgery.

COLIC OBSTRUCTION NOT DUE TO PRIMARY COLIC MALIGNANCY

Aside from the thirty-five cases of obstruction due to colic malignancy there were nineteen due to a variety of causes. In seven cases, obstruction was caused by malignancies arising elsewhere in the pelvis and involving the colon secondarily, four were blocked by pelvic inflammatory lesions, five by volvulus of the sigmoid, one by a regional transverse colitis, one by impaction of feces following a barium meal given a patient with bleeding ulcer, and one by a prolapse of the rectosigmoid (Table II).

TABLE II

COLIC OBSTRUCTIONS ASIDE FROM PRIMARY COLIC MALIGNANCIES

OBSTRUCTING MECHANISM	NO. OF CASES	MANAGEMENT		DEATHS	
		TYPE	NO.	NO.	%
Pelvic neoplasms[1]	7	Transverse colostomy	6	0	0
		Inguinal colostomy	1	0	0
Inflammatory obstruction of pelvic colon[2]	4	Transverse colostomy	4	0	0
Regional colitis, splenic flexure	1	Transverse colostomy	1	0	0
Volvulus of sigmoid	5	No therapy, terminal	1	1	100
		Exteriorization in L.L.Q.	2	1	50
		Colostomy of sigmoid through high transverse incision	1	0	0
		Exteriorization through high transverse incision	1	1	100
Impaction of barium	1	Transverse colostomy	1[3]	1	100
Rectosigmoid prolapse	1	Transverse colostomy	1	0	0
Total	19			4	21%

[1]Two cases each of carcinoma of cervix and ovary; one case each of carcinoma of prostate and uterus; one neurofibroma.

[2]Two cases of diverticulitis; one case of tuberculosis of sigmoid; one case of pelvic abscess from salpingitis complicated by perforation of the cecum requiring suture; recovery.

[3]Death from recurrent severe gastric hemorrhage nine days postoperatively.

INFLUENCE OF BARIUM MIXTURE IN INCREASING THE DEGREE OF OBSTRUCTION

It has been stressed elsewhere[8] that administration of barium mixture by mouth to patients with partial small bowel obstruction is likely to render that obstruction complete. In the present series of large bowel obstructions are nine cases in which the obstructions were not complete until the introduction of barium mixture either by mouth or as a barium enema, becoming complete within a few hours thereafter. There were eight other cases in which complete obstruction occurred and in which barium had been administered before development of complete occlusion, but in these other cases it was felt that the barium mixture probably played no part in rendering the obstruction complete, for roentgenograms taken at the time of obstruction failed to show barium near the site of closure, or failed to show any barium at all. The cases are summarized in Table III. Eight of the patients with obstruction by barium underwent transverse colostomy, and one was decompressed by a Miller-Abbott tube and was later subjected to right hemicolectomy for a lesion of the hepatic flexure. It is noteworthy that one patient had no evidence of organic obstruction at subsequent autopsy; he died nine days after operation, of recurrent massive hemorrhage from a duodenal ulcer. Temporary occlusion had been on the basis of fecal impaction.

TABLE III

PRODUCTION OF COMPLETE COLIC OBSTRUCTION BY THE USE OF BARIUM MIXTURE FOR ROENTGEN EXAMINATION

CAUSE OF OBSTRUCTION	NO. OF CASES	MANNER OF ADMINISTRATION
None (impaction)	1	Meal
Sigmoid diverticulitis	1	Enema
Carcinoma of cervix uteri	1	Enema
Carcinoma of hepatic flexure	1	Meal
Carcinoma of splenic flexure	1	Meal
Carcinoma of descending colon	1	Enema
Carcinoma of sigmoid colon	3	One meal, two enemas

Eight additional patients were given barium enemas cautiously without complication resulting.

RESULTS OF THERAPY

Primary Resection in the Presence of Obstruction.—In two instances in the recent past it has seemed at operation that removal of the lesion was possible despite obstruction. In the first of these, a napkin-ring obstructing carcinoma was exposed through a left lower rectus incision, this approach having been used because of the suspected presence of volvulus (see footnote,[2] Table I). The lesion was lifted onto the abdominal wall with no dissection necessary. Due to lack of fatty tags, the bowel itself was fixed to the abdominal wall with fine silk sutures and decompressed at the end of the operation with a catheter secured

with a purse-string suture; the lesion was cut away several days later. Presumably due to placement of sutures into the tremendously stretched and thinned gut wall, the patient developed a chronic adhesive peritonitis, with recurring obstruction of large and small bowel, and ultimately died two months after admission. This patient's death was also reported as a small bowel obstruction death.[8]

In a second case, not listed in the tables because obstruction was partial, medical decompression, for preparation for primary resection of a sigmoid cancer, was found to be incomplete at operation. The colon was therefore decompressed by the Wangensteen aseptic decompression trocar,[31] and resection was performed. The patient died six days later with separation of the suture line.

Transverse colostomy was considered in both cases and should have been used in both.

Transverse Colostomy for Acute Colic Obstruction.—In all, transverse colostomy was used in thirty-eight cases of acute left colic obstruction, of which twenty-five were due to intrinsic cancer. In this series there were three deaths, two in the intrinsic cancer group and one in which obstruction was due to fecal impaction alone, a mortality rate of 7.9 per cent. Transverse colostomy was regularly used in the worse cases, and the procedures were performed by a group of over a dozen house officers and staff members, and were thus not concentrated in the hands of one or two individuals, factors tending to make more evident the relative safety of the method. Both of the cancer obstruction deaths were due to perforations which occurred prior to surgery, one to perforation of the cecum, which was closed through an accessory right lower rectus incision at the time of transverse colostomy, and the other to perforation of a descending colic lesion with liver abscesses and peritonitis. The third death resulted from recurrent massive hemorrhage from a duodenal ulcer nine days after surgery.

One complication was recognized on three occasions, namely, adhesion of small bowel to the site of apposition of colon and abdominal wall, with or without herniation. Once the patient was returned to the operating room a day after surgery for return of a segment of ileum to the abdomen; once the abdomen was opened and a segment of ileum freed of adhesions to this area in a patient who had had a volvulus of the sigmoid colon drained by transverse colostomy incision; once adhesions of small bowel to this region were found incidentally at post mortem.

Inguinal Colostomy for Acute Colic Obstruction.—In three cases, inguinal colostomy was used to relieve low-lying obstructions. Death resulted in none of these.

Procedures for the Relief of Volvulus of the Sigmoid.—The remaining four left colic decompressive procedures were done for volvulus of the sigmoid colon, in which the threat of sigmoid strangulation dictates more than transverse colostomy. One of these patients died early,

apparently of atelectasis, and one died from peritonitis seven days after operation, apparently secondary to retraction of one loop of the colostomy remaining after a Rankin[21] obstructive type of resection.

The deaths from volvulus occurred early in the present period of study, while the recoveries are of recent occurrence. Management of choice seems to have been achieved in the last case (Fig. 2). Prior to surgery, a soft rectal tube was inserted twelve inches and secured with tape; the tube kinked on itself in the upper rectum, but it was easily delivered into the lower sigmoid by manipulation from within the abdomen after detorsion had been accomplished. A high spinal anesthetic was given in the vain hope it might cause sufficient colic contraction to eliminate the need for surgery.[24] The huge sigmoid loop was delivered through a long left rectus incision and readily emptied of 2,700 c.c. of gas and fluid through the already placed rectal tube (measured by Wangensteen suction siphonage apparatus). Clamps were placed across the proximal and distal limbs; the mesentery was cut, securing hemostasis by silk stitches, and the wound was closed with steel wire sutures, leaving a double-barreled colostomy, clamped. A catheter was fixed into the proximal loop with a purse-string suture, but otherwise no sutures were placed in the bowel. Uneventful recovery resulted, and simple closure of the colostomy was accomplished later.

Procedures Used in Right Colic Obstruction.—In six cases complete obstruction occurred in carcinoma of the right colon. Three patients were treated by terminal double-barreled ileostomy with insertion of a catheter through the ileum and into the cecum, one was given an appendicostomy, and two decompression by Miller-Abbott tube, each of these last two being successfully subjected three days thereafter to hemicolectomy of the right side with primary end-to-end ileotransverse colostomy.

Two deaths occurred in the right colic obstruction group; in one case obstruction occurred at the hepatic flexure from metastasis from a cecal primary lesion, and a perforation of the ascending colon was sutured and terminal ileostomy performed at operation, a suspension of 2 Gm. of sulfathiazole in one ounce of water being left in the abdomen. The patient died nineteen days later; autopsy showed a clean abdomen and a liver almost completely replaced by cancer. In the second case, ileostomy was performed for carcinoma of the ileocecal valve in the presence of massive ascites. The patient died three days later in convulsions. No autopsy was allowed.

Summary of Results of Operative Procedures.—The results of the operative procedures outlined are tabulated in Table IV.

OBSERVATIONS ON INTRALUMINAL PRESSURES IN COLIC OBSTRUCTION

In most of the cases of colic obstruction of the left side the intraluminal pressure was determined at the time of transverse colostomy.

TABLE IV

COMPARISON OF THE RESULTS OF VARIOUS PROCEDURES IN THE RELIEF OF ACUTE COMPLETE COLIC OBSTRUCTION

	NO. OF CASES	DEATHS NO.	DEATHS %
Simple obstructions	49	6	12.2
Transverse colostomy	38	3*	7.9
Inguinal colostomy	3	0	0
Primary Mikulicz for carcinoma of sigmoid	1	1	100
Double-barreled ileostomy	3	2	66
Appendicostomy	1	0	0
Miller-Abbott tube decompression followed by right hemicolectomy	2	0	0
Miller-Abbott decompression followed by Rankin excision of transverse colon	1	0	0
Volvulus of the sigmoid	4	2	50
Exteriorization	3	2	66.7
Colostomy (sigmoid)	1	0	0
Total	53	8	15.1

*Upon laparotomy, two of these patients were found to have perforations. The other died of duodenal hemorrhage nine days later.

In the sigmoid colostomies and the right colic obstructions, as well as in decompressions by the Miller-Abbott tube, it was usually not feasible.

In all, thirty-four determinations were made. Although the highest value, 34 cm. of water, was found in a patient with carcinoma of the sigmoid colon, the average of this group is not significantly different from that in other parts of the colon. The average of the thirty-four determinations was 14 cm. of water, the minimum was 1 cm. In both the fatal cases with perforation, the pressure was 20 cm. of water. In the group with volvulus of the sigmoid colon, the maximum pressure was 15 cm. of water, suggesting that the symptoms and findings of pain and peritoneal irritation depend more largely on the twist, with pull on the mesentery and interference with blood flow there, than on any ischemia secondary to increased intraluminal tension.

OBSERVATIONS ON THE INCIDENCE OF VOMITING AND OF SMALL BOWEL DISTENTION IN ACUTE COLIC OBSTRUCTION

Prior to the early 1930's, it was the general opinion that fecal emesis in the presence of bowel obstruction indicated that the obstruction lay in the colon. In 1934, however, Wangensteen pointed out that the converse is true, namely, that fecal emesis usually indicates small bowel obstruction, and that in the majority of instances the ileocecal valve prevents reflux into the ileum, thereby preventing prominent vomiting and particularly vomiting of fecal character.[29] He and Sperling showed that in many instances the valve is sufficiently competent not only to prevent vomiting but also to convert the simple colic obstruction into a "closed loop" type of obstruction, with rapid rise in intracolic pressure and ischemic necrosis, and consequent perforation of the wall of the cecum.

Such competency of the ileocecal valve has been adopted by many radiologists as an aid in the diagnosis of colic obstruction,[23] absence of gas visible in the ileum confirming the impression of colic occlusion. On the part of certain radiologists there has been a tendency to look with great doubt on the diagnosis of large bowel obstruction if gas is visible in the ileum at all.

A.

Fig. 4.—Examples of varying amounts of gas visible in the small bowel in cases of colic obstruction. Scout films of the abdomen.
A) Group *1*—Gas visible in the ileum but in insufficient amount to produce definite distention (29% of series).
B) (p. 728) Group *2*—Definite small bowel distention, but colic distention predominant (32% of series).
C) (p. 729) Group *3*—Small bowel distention more marked than colic distention (7% of series).

With a view to evaluation of the diagnostic importance of gas visible in the scout film in colic obstruction cases, the films have been carefully reviewed in the present series.*

For purposes of classification, cases have been divided into four categories on the basis of preoperative roentgen findings:

0. Those patients in whom no gas can be seen in the films in the small bowel, or in whom the presence of it is equivocal (Fig. 1).

*With the generous assistance of Dr. O. H. Wangensteen, Chief of the Department of Surgery, and Dr. L. G. Rigler, Chief of the Department of Radiology, at the University of Minnesota School of Medicine.

1. Those with gas visible in the ileum, but in insufficient amount to produce definite distention (Fig. 4*A*).
2. Those in whom there is definite small bowel distention visible on the film, but in whom the colic distention dominates the picture as a whole (Fig. 4*B*).
3. Those in whom the distention visible involves predominantly the small intestine, the colic distention being definitely less in degree (Fig. 4*C*).

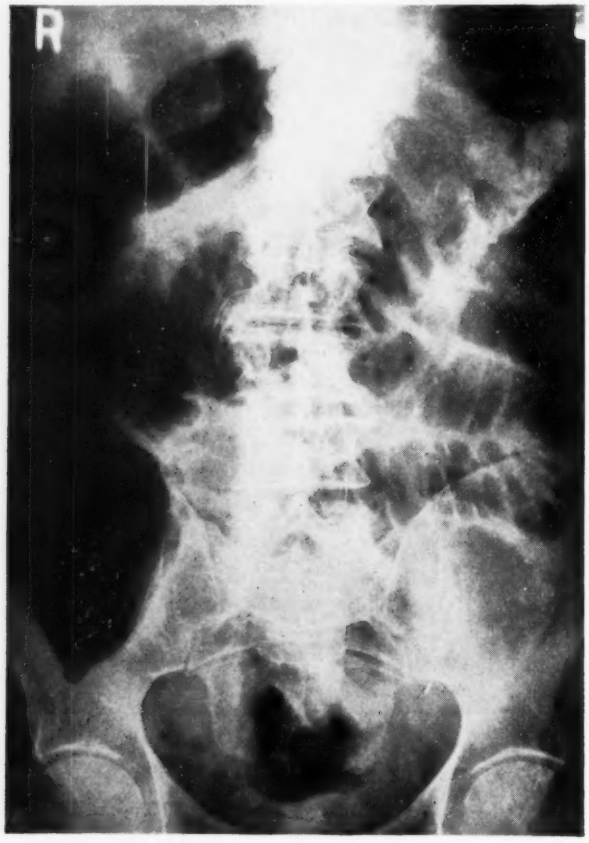

Fig. 4*B*. (*For legend see p. 727.*)

In reviewing these roentgenograms it is to be emphasized that the presence of gas in the ileum may be explained as well on the basis of stasis in that viscus as on the basis of incompetency of the ileocecal valve, except in those instances in which the ileac distention is extremely marked. Films were reviewed on fifty-two cases, two films having been lost.

In such a study it seemed important to evaluate the extent of the vomiting also as a possible measure of the competency of the ileocecal valve. Vomiting was considered significant only if it occurred on

three occasions or more. Those who had had stercoraceous emeses were so listed. The observations concerning vomiting have been culled from the hospital records of these patients; the data would obviously be of greater significance if based entirely on personal observations.

Certain cases were excluded from the vomiting study because of obstruction on some other basis, such as involvement of the ileum in the tumor or active duodenal ulcer. Others were excluded from the roentgen study because of peritonitis, carcinomatosis, or ileac obstruction.

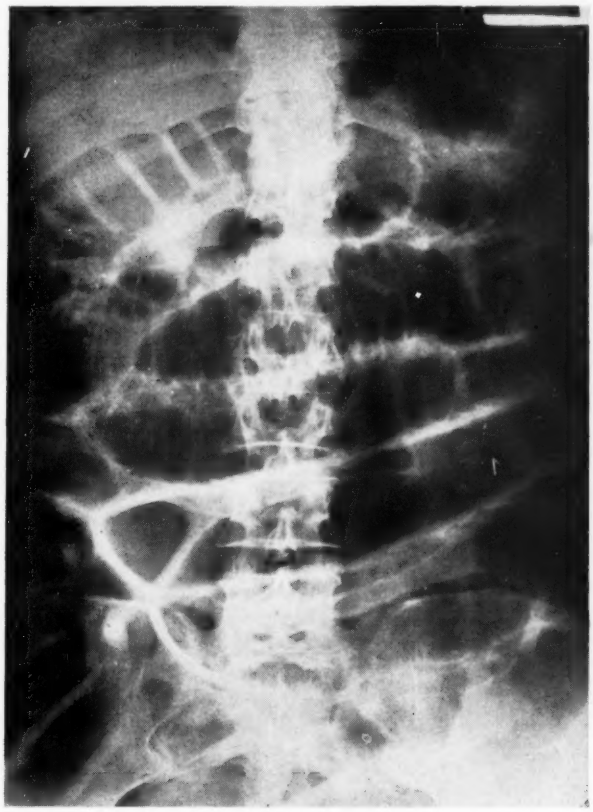

Fig. 4C. *(For legend see p. 727.)*

The data are presented in Table V. It is apparent that about one-half the patients vomited three times or more and that fewer than 8 per cent had vomiting of fecal character. As for the roentgen findings, a little more than two-thirds of the group presented some definite evidence of gas in the ileum, about one in three presented real ileac distention, and in fewer than 8 per cent was the small bowel distention more striking than the distention of the colon.

The correlation between degree of small bowel distention apparent roentgenologically and the amount of vomiting was not marked. About one-third of the patients who vomited showed no intraileac gas on the

TABLE V

THE INCIDENCE OF VOMITING AND OF ROENTGENOLOGICALLY PERCEPTIBLE GAS IN THE SMALL BOWEL IN COLIC OBSTRUCTION

SITE OF LESION OR TYPE OF LESION	INCIDENCE OF VOMITING					ROENTGEN EVIDENCE OF GAS IN THE SMALL BOWEL				
	NO. OF CASES	VOMITING THREE TIMES OR MORE				NO. OF CASES	NO GAS 0	GAS IN SMALL GUT 1	DISTENTION OF SMALL GUT 2	DISTENTION OF SMALL GUT PREDOMINANT 3
		TOTAL		FECAL VOMITING						
		NO.	%	NO.	%					
Rectum	4	4	100			3[1]		1	2	
Sigmoid	19	8	42.1	3	15.8	16[2]	8	4	3	1
Descending to transverse colon	5[3]	2	40			3[4]		2	1	
Right colon	5[5]	3	60	1	16.6	4[6]			2	2
Volvulus of sigmoid	5	3	60			4[7]	2	1	1	
Impaction or prolapse	1[8]	1	100			2	1		1	
Inflammation or extracolic	12	5	41.7			9[9]	2	4	3	
Total	51	26	51	4	7.8	41	13 (31.7%)	12 (29.3%)	13 (31.7%)	3 (7.3%)

[1]The x-rays were lost; one case, omitted.

[2]Three omitted; one because the x-rays have been lost, one because of perforation, and one because of carcinomatosis; the latter two showed definite distention of the ileum.

[3]One case was omitted because the small intestine was involved in the cancer.

[4]Two cases were omitted because of carcinomatosis; one showed some gas in the ileum, the other definite distention. A third was omitted because the ileum was involved in the cancer.

[5]One case was omitted because the ileocecal valve was involved.

[6]One case was omitted because the ileocecal valve was involved, another because of peritonitis; in both the small intestinal distention dominated the picture.

[7]One was omitted because of perforation; there was no gas visible in the ileum.

[8]One case was omitted because of duodenal ulcer.

[9]Three cases were omitted because of carcinomatosis; one showed no gas, one a little, and one definite distention of the ileum.

The remainder in this group were relieved by colostomy, and it is therefore assumed that the ileum was not obstructed by the lesions concerned.

N.B. If all those with either carcinomatosis or possible peritonitis were excluded from the vomiting study series, the total number of cases would be 42, with 22 vomiting three times or more (52 per cent), and 3 of these having stercoraceous emeses (7.1 per cent of whole group of 42).

films. This amount of vomiting therefore must be explicable as reflex in nature. All of those whose vomiting was of fecal character also had marked ileac distention visible by scout film. About two-thirds of those with definite ileac distention also vomited three times or more.

COMMENT

It is apparent from the figures of Table V that competency of the ileocecal valve is usually but by no means invariably present. There was definite regurgitation into the small bowel in about one-third of this series of patients, and consequential vomiting occurred in about 12 per cent. Five out of forty-one patients free of complications such as carcinomatosis, peritonitis, or involvement of the ileum in the lesion presented a clinical picture which could readily have been interpreted as small bowel obstruction, and fecal vomiting occurred in at least three of them. The conclusion is apparent that the presence of vomiting, even if persistent and fecal in character, should not cause the examiner entirely to overlook the possibility of large bowel obstruction, even while admitting that these symptoms are far more likely to indicate an occlusion in the small intestine.

It will be recalled that in 1934 Wangensteen first pointed out that the character of the vomiting should be of great help to the clinician in differentiating small from large bowel obstruction. He correctly stressed that stercoraceous emesis is not evidence of colic obstruction, but, on the contrary, that it is strong evidence in favor of small bowel occlusion, the factor preventing such emesis in colic obstruction being the customarily competent ileocecal valve.

The evidence presented in this communication is, in the main, in agreement with Wangensteen's teaching. Whereas almost 100 per cent of complete obstructions in the ileac region in dogs result in stercoraceous vomiting in four and one-half to five days, just as is the case in clinical patients, in only four patients in fifty-one (7.8 per cent) did such fecal vomiting occur in the present group of colic obstructions.

The teaching of Wangensteen regarding absence of small bowel distention in colic obstruction is also fairly well borne out in the present study, for careful review of the films has shown perhaps small quantities of gas in the ileum, but no real distention in almost two-thirds of these patients, and in only three out of forty-one cases (7.3 per cent) was the distention seen on the film situated predominantly in the small intestine. This is in marked contrast to small bowel obstruction, in which, in the experience here, almost 90 per cent of the patients showed marked ileac distention.

The levels of intraluminal pressure here reported are not as high as one found earlier by Wangensteen,[27] 52 cm. of water, but many of them are more than adequate to cause the changes in the cecal wall which Sperling described with low levels of sustained pressure,[26] or the areas of ischemic necrosis which a sustained 10 cm. pressure causes

in the cecal appendage of the rabbit.[9] These observations, combined with a consideration of the frequency of competence of the ileocecal valve, only tend to emphasize that acute colic obstruction should be regarded as a surgical emergency.

Presence of fecal vomiting and marked ileac distention might at first suggest that, the ileocecal valve being incompetent, perforation of the cecum may be prevented by ready regurgitation into the ileum. That such is not always the case has been demonstrated by one case prior to the present study period and reported by Rigler; perforation of the cecum in this patient occurred in the presence of marked ileac distention and a presumably incompetent valve.

The anatomic basis for incompetency of the ileocecal valve has been attributed by Buirge to shortness of one or the other of the lips. In this series, on examination by him, the patient with right colic obstruction, who vomited fecal material, was found to have a valve with both lips defective.

A few years ago primary anastomosis in the face of obstruction in the small intestine was considered to be a highly hazardous procedure, and yet it has proved to be feasible and relatively safe in a series of strangulating obstruction cases.[7] The possibility that proper application of the closed anastomotic technique to the obstructed colon may prove similarly successful must be considered. Factors tending to dictate caution in this regard are the much greater degree of distention usually found above colic obstructions, the relative thinness of the wall even before distention occurs, the more solid character of the content, and probably the heavier bacterial content in the lumen and wall. Whether these handicaps can be overcome remains to be seen. In any case, diversion of the fecal stream temporarily from the colon is free of many of the dangerous and distressing consequences of ileostomy, and the urgency for primary anastomosis in the colon is therefore less great than in the small intestine.

The data presented concerning the absence of mortality from the operative procedure of transverse colostomy in acute obstruction are the more impressive when it is recalled that the risk of cecostomy at this hospital under the same senior staff was almost 50 per cent. Transverse colostomy at first thought appears a more extensive procedure than cecostomy or appendicostomy, but, because of the almost uniform mobility of the transverse colon, in sharp contrast to the cecum and often to the sigmoid, it can regularly be lifted onto the abdominal wall with no dissection whatever. A second factor adding to the relative safety of this procedure is the almost uniform presence of fatty tags and omentum at this point by which the colon may be approximated to the cut edges of the parietal peritoneum and rectus sheath. In the greatly distended cecum, on the contrary, fixation must be attained by placement of sutures into a paper-thin cecal wall, which invites leakage with every stitch.

CONCLUSIONS

1. The mortality rate for relief of acute colic obstruction in fifty-three cases at the University of Minnesota Hospitals from Jan. 1, 1938, to Jan. 1, 1944, was 15.1 per cent.

2. The incidence of acute colic obstruction in cancer of the colon in this period was 9.54 per cent of 367 cases.

3. Distention of the small intestine, as seen by roentgen picture, was present in sixteen out of forty-one cases (39 per cent). It seemed to be more likely to occur and more marked in right than in left colic obstructions. Three of these sixteen patients had fecal vomiting and five presented a clinical and roentgen picture which could readily be confused with small bowel obstruction. Vomiting three or more times occurred in 51 per cent of fifty-one patients, but so many of these showed no distention of the small intestine on the film that this amount of vomiting is considered reflex rather than evidence of incompetency of the ileocecal valve.

4. The ileocecal valve was competent in 61 per cent of this series, a sufficiently large proportion of the cases to make the threat of a "closed loop" colic obstruction a very real one. Acute complete colic obstruction is therefore a surgical emergency.

5. Barium mixture should not be given to patients with partial colic obstruction, for it may render it complete.

6. In those thirty-eight patients treated by transverse colostomy the mortality rate was 7.9 per cent. In two of the fatal cases perforations had already developed at the time of admission to the hospital, and the third patient died later of a gastric hemorrhage.

7. The mortality referable to the performance of transverse colostomy in this series was zero.

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CAST AND PRECAST CARTILAGE GRAFTS

Their Use in the Restoration of Facial Contour

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THE exact restoration of facial contour has always been a difficult problem. This is especially so in those instances where large portions of the facial skeleton have been lost. The practice of most surgeons has been to model rib cartilage as nearly as possible to the shape desired and then insert this solid object under the skin to replace the lost facial bone. This procedure has drawbacks. In major contour defects there is not enough cartilage available nor is it in large enough pieces to serve the purpose. In the time at one's command, exact modeling is difficult. It is often hard to secure firm satisfactory fixation of the graft in the desired location. After insertion the graft may warp. In spite of these objections the method has been the best available. Autogenous cartilage is preferable to bone because it usually does not absorb, and because it is more easily modeled. Although many different sorts of foreign material have been used with some success, it is generally accepted that when available, living tissue is preferable.

Recognizing the limitations of the methods heretofore used, I would like to report a method which has been most gratifying. Facial contour can be *exactly* restored by the implantation of fine particles of autogenous cartilage under the subcutaneous tissues and the application of a form over the area, which holds the particles in the desired contour while they heal together. The cartilage is thus cast in an exact replica of the part.

This method is based on experimental work reported in July, 1941.[1] In brief, autogenous rib cartilage was chopped into particles about $\frac{1}{16}$ inch square and then seeded over the rectus fascia in dogs. In one and one-half years it was possible to recover a thin sheet of glistening, translucent, cartilaginous-appearing material. This sheet of material had the appearance and springlike quality of cartilage. On microscopic examination it was found that the small pieces of cartilage had adhered to one another by fibrous tissue (Fig. 1).

From this experimental work it seemed feasible to attempt to cast cartilage particles into a desired shape as they healed together. If this were possible, it would have several advantages over previous methods of restoring lost skeletal support. It would be possible to reproduce contours exactly. Larger losses could be repaired since one could, if necessary,

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use all the costal cartilage available and cast it in one large mass. In addition, the same amount of cartilage would fill a much larger defect than a solid graft, since a certain amount of space would be taken up by the fibrous tissue binding the small particles together. It also

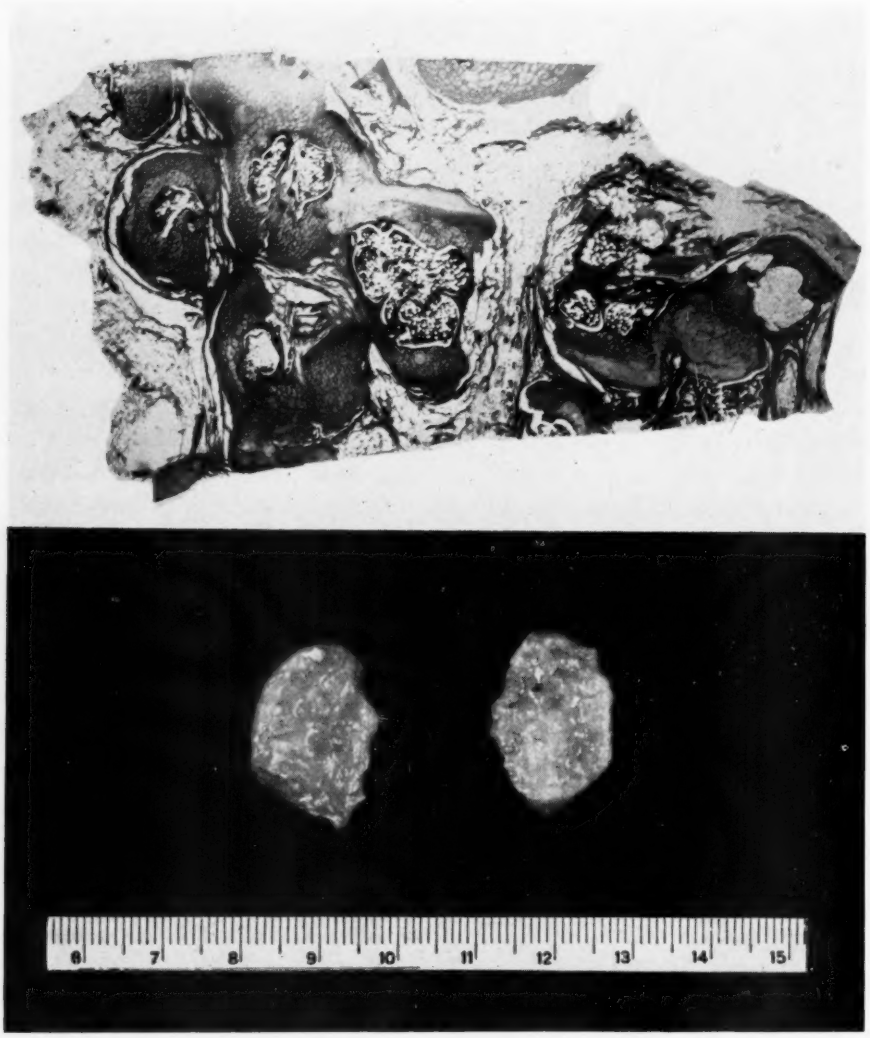


Fig. 1.—The microscopic and gross appearance of cartilage grafts produced in dogs by the implantation of cartilage particles in subcutaneous pockets. These grafts were removed one and one-half years after the chopped costal cartilage was implanted.

seemed that fixation would be easier, for if one denuded the remaining bone about the defect and held the solidifying cartilage accurately in place a broad firm attachment might be secured.

While at work on this problem our conclusions were strengthened by hearing a paper presented by Peer and since published,[2] in which, following my experimental work, he had filled various depressions about the face with small particles of cartilage. This procedure he

designated as "diced cartilage grafts"—a catchy, quite descriptive term. He had, however, made no attempt to cast these particles accurately. He did find, as one would expect, that particles of cartilage behaved no differently in human beings that I had already reported was the case in dogs.

CAST CARTILAGE GRAFTS

In order to cast the healing cartilage particles into exact facial contours, an accurate negative form of the part desired must be used to hold the graft in shape. This form is best made of some resilient material for it will then by its elasticity gradually mold the implanted cartilage

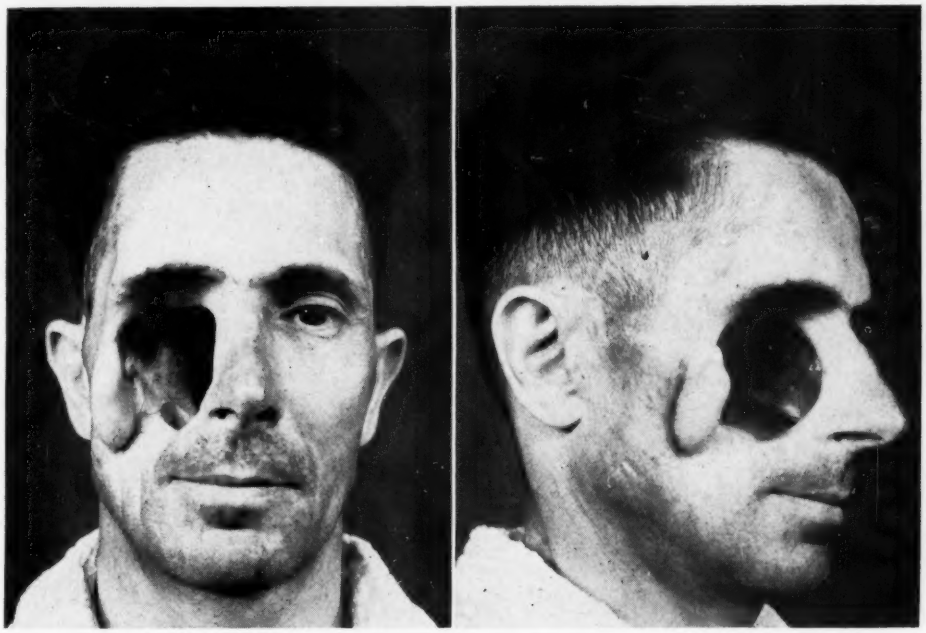


Fig. 2.—Soft tissue and bony defect following radical extirpation of extensive advanced carcinoma of antrum. Free of recurrence for one and one-half years.

into accurate shape. We have used a latex mold for this purpose. It is fairly rigid but does have some resilience. The steps necessary to secure the latex form are obvious to those familiar with the methods used in producing wax or plaster models, but for the sake of clarity they may be outlined as follows:

Method.—

1. An impression or negative of the deformed face is made. This includes the entire face. It may be made of plaster or any one of the agar base materials.

2. From this negative a positive is poured in wax or plaster depending upon the material used for the negative. This gives an exact reproduction of the deformed face as shown in Fig. 3.

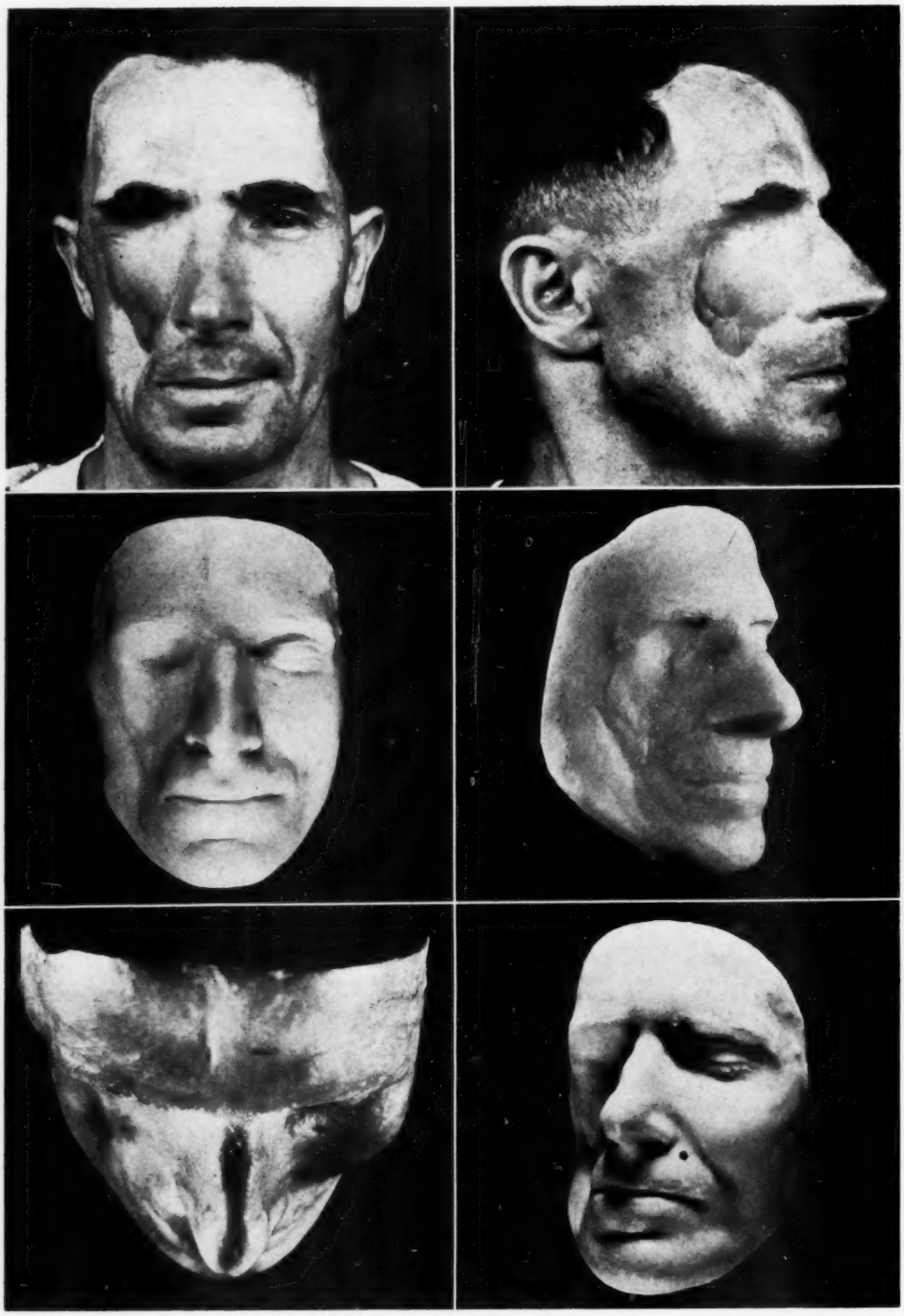


Fig. 3.—Appearance of patient shown in Fig. 2 after soft tissue restoration by means of right forehead flap for lining, and arm flap and adjacent skin of cheek for external covering. A marked distortion of facial contour is present. The extent of this sinking in of the face is best noted in the masks photographed from above and obliquely. Notice that the right infraorbital ridge and the malar eminence are absent.

3. On this mask of the face, the missing part is restored in modeling compound until normal symmetry is obtained (Fig. 4*A*).

4. A negative is made of the restored face and from this a plaster positive is made. This reproduces the face restored as finally desired (Fig. 4*B*).

5. About ⅛ to ¼ inch of modeling compound is then layered evenly over the mask restored in modeling compound (Fig. 4*A*) and a plaster negative made of this.

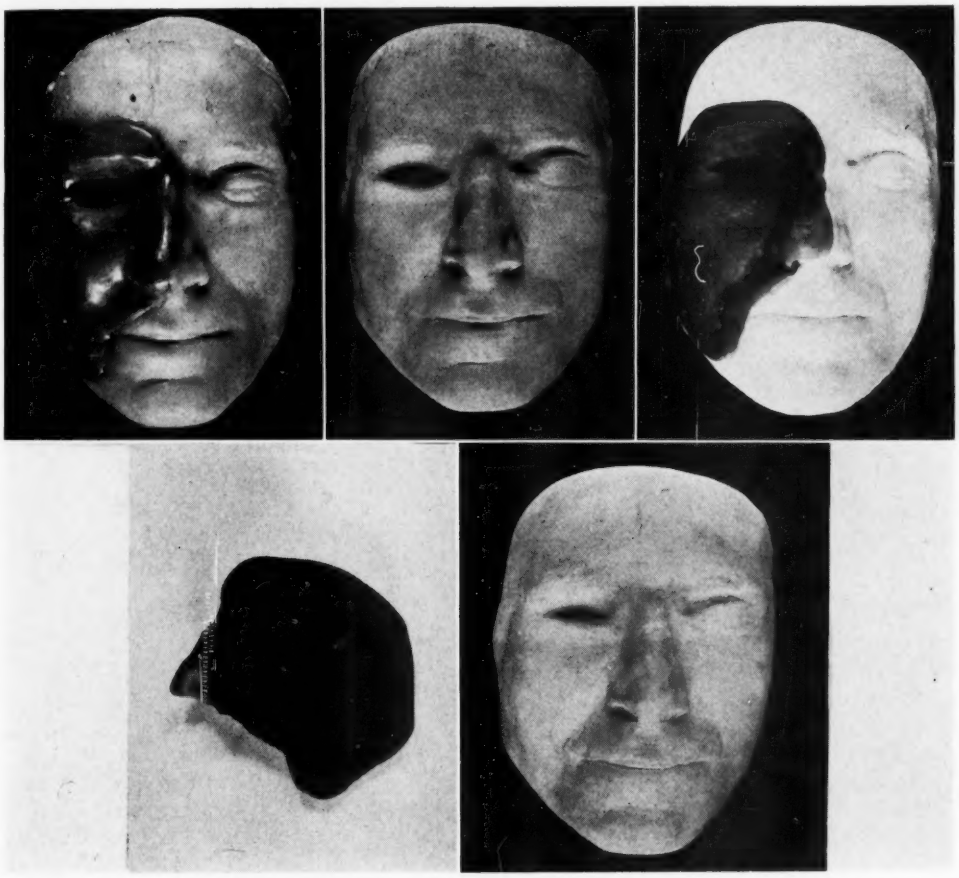
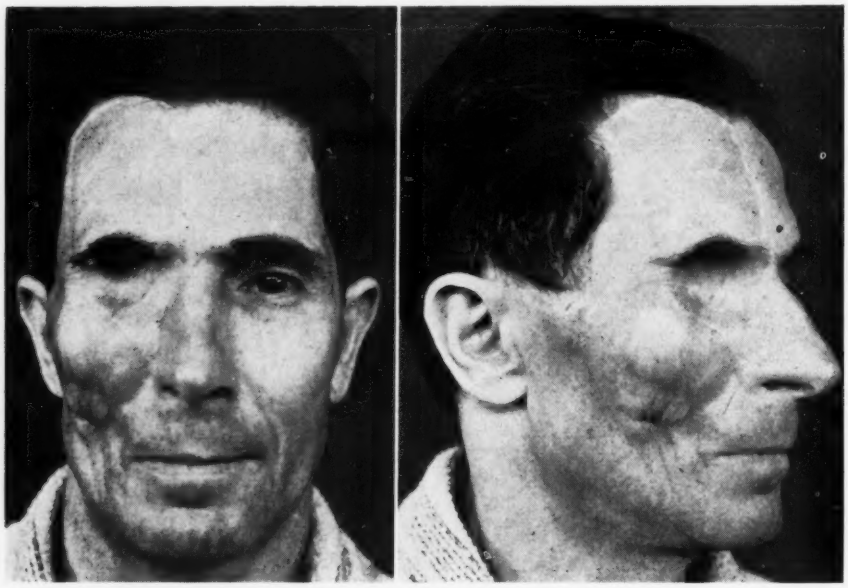


Fig. 4.—*A*, The defect has been restored in a mask with modeling clay and the surface of the restored area built up about ¼ inch. *B*, A plaster mask of the desired contour. *C*, The latex form fits the restored mask exactly. D, The negative side of the latex form which fits exactly as the plaster model *e*.

6. This plaster negative is superimposed on the normal plaster mask, a hole drilled into the ⅛ to ¼ inch space between the two, and the space filled with liquid latex which is vulcanized at 37° C. for twenty-four hours.

7. A rubber mold, ⅛ to ¼ inch thick, of the normal restored face is then ready for use (Fig. 4, *c* and *d*).

The surgical steps in forming the graft are simple. As much autogenous costal cartilage as needed is removed and chopped into small pieces about 1/16 to 1/8 inch square. An incision is made peripheral to the defect, and a subcutaneous pocket whose margins widely overlap the surrounding normal skeleton prepared. This pocket is filled with



A.

B.

Fig. 5.—Appearance of patient after cartilage graft has been cast in place. In view from above, the missing infraorbital ridge and malar eminence noted in Fig. 3 are now restored.

cartilage particles which rest on bone around the periphery and the incision closed. The particles are roughly molded into approximate desired contour and the latex mold applied to complete the final molding into exact shape. Firm fixation of the mold is obtained by appropriate dressings and the healing graft undisturbed for seven to ten days. The mold is worn for about four weeks. The graft will then be solid and firmly adherent (Figs. 5 and 6).

Fig. 6.—Appearance of patient five years after resection of original carcinoma and six months after cast cartilage graft.

The use of this method is illustrated in detail in the following case report.

CASE REPORT

M. E. (S. M. H. No. 149347), a white, male laborer, aged 52 years, first entered the hospital on Jan. 26, 1939. During the previous six months he had suffered with pain and swelling of the right cheek. During that time most of the right maxillary teeth had been extracted, "nasal polyps" had been removed, and the right antrum had been irrigated repeatedly. He had been in another hospital on several occasions during these six months with attacks of bloody nasal discharge, swelling of the right cheek, and fever. Shortly before entry the remaining teeth in the right upper jaw had been extracted and most of the antral floor had come out with the teeth. A biopsy of the material removed diagnosed it as epidermoid carcinoma. He was then referred to us for treatment.

On admission to the Strong Memorial Hospital there was an obvious firm swelling of the whole right cheek. The right nares was filled with necrotic purulent material. The right maxillary alveolar ridge was replaced by fungating vascular tissue which protruded into the oral cavity. This bled easily when touched. The right antrum did not transilluminate. A mass of tumor tissue could be seen protruding through the posterior choanae into the right nasopharynx. X-ray showed

destruction of the floor and lateral wall of the right antrum and some destruction of the right malar bone. There was also some destruction of the outer wall of the right nasal cavity. A biopsy of the tissue protruding into the mouth showed squamous cell carcinoma.

He was given 2,200 R x-ray treatments over the right antrum. During the next four weeks the external swelling decreased a great deal and the tumor in the mouth regressed. On March 23, 1939, the skin of the right cheek was turned laterally as a flap. The anterior wall of the antrum was replaced by tumor and the infraorbital plate was invaded. The antral cavity was filled with soft necrotic tumor. This was removed and the eye enucleated leaving a portion of the uninvolved upper lid. There was no question that tumor remained and the cavity was left open for radiation therapy. Three weeks later a radium pack was placed in the cavity and a total dose of 1,600 mg. hr. given. As there was still tumor tissue along the alveolar ridge this was burned away by cautery about two weeks later. The patient was then followed for about two months and a small recurrence in the lateral superior portion of the cavity was excised by cautery, and following this 780 mg. hr. of radium were applied. He was then observed frequently for a year and had no recurrence (Fig. 2).

The defect was then closed by a series of surgical steps. These consisted in the transfer of a delayed flap from the right half of the forehead to supply an epithelial lining for the anterior wall of the cavity. The forehead skin was replaced by grafting the area with a thick dermatome graft from the infraclavicular region. The skin covering of the cheek was supplied by the remnant of facial skin which had been saved and by a delayed flap from the right upper arm. The opening into the mouth cavity was closed by mobilizing mucosa adjacent to the defect. After eleven major and minor operative steps the cavity was finally closed externally and intraorally. This of course left a large cavity where the antrum had once been which communicated with the nasopharynx and the right nasal cavity.

The closure was completed in July, 1941, almost two and one-half years after the antral growth was first resected. Closure of the cavity improved the comfort of the patient, since he no longer had to wear a dressing, but he was still disfigured because of the absence of the eye and the marked depression of the cheek. The flap transferred from the arm had been provided in excess so that an attempt to restore the bony contour could be made. However, this attempt had to be delayed because of a persistent sinus at one of the lines of closure. The sinus was finally closed by excision in November, 1942, after two previous attempts had been unsuccessful.

In March, 1943, four years after original radical resection, the final operation for restoring the skeletal contour was performed. All of the costal cartilage on the right side was removed through an oblique incision. This was chopped into small particles about ⅛ inch square. An incision about 1 inch long was made in normal tissue lateral to the position of the right malar eminence. Through this opening the inner and outer layers of skin and subcutaneous tissue which had been used to close the defect were dissected free medially to the nose, downward to the nasolabial fold, and upward to the superior rim of the orbit. This was accomplished without perforation of the inner lining as was evidenced by the fact that no blood could be recovered by suction from the right nasal cavity or nasopharynx. The cartilage particles were introduced into the space created by dissection and the small lateral incision sutured. The latex mold previously made was applied to mold the cartilage particles into the contour of the malar eminence and inferior orbital rim. This was held in place by a head dressing. The mask was removed on the fifth postoperative day. There was a moderate accumulation of serum under the skin over the mass of cartilage. This was aspirated and the

form reapplied. The mask was worn for three weeks and at that time the cartilage was firm and attached; the form was discontinued. The patient has been seen at intervals since. The graft has not shrunken, has maintained its shape, and is an integral part of the face. Fig. 6, the photograph showing final appearance, was taken six months after the cartilage was cast in place. The patient was last seen almost one year after the cartilage transplant, and there had been no shrinkage.

PRECAST CARTILAGE GRAFTS

There are certain locations where cartilage grafts of extreme thinness and elasticity would be desirable. Such grafts could be used to duplicate the complicated contours of a lost ear, the missing alar cartilages of the nose, or the tarsal plate of an eyelid. The usual struts of cartilage used in restoring lost nasal framework are thick and stiff.

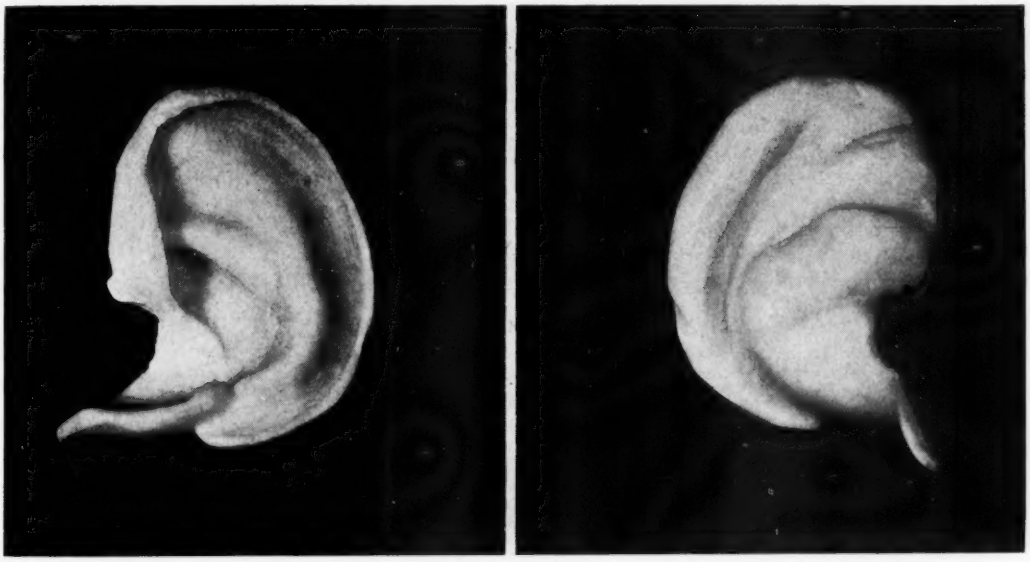
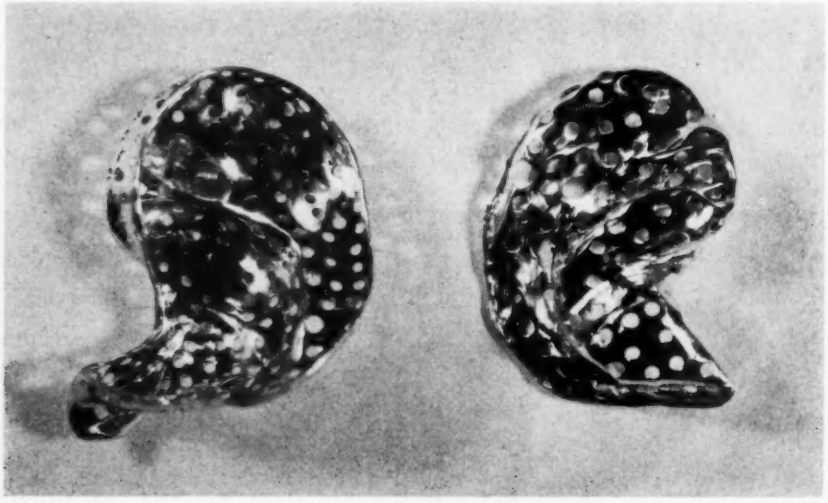


Fig. 7.—Wax model of an ear cartilage. This was constructed by pouring wax into a plaster form reproduced from a cadaver ear cartilage which was selected for size and shape to correspond to the ear desired.

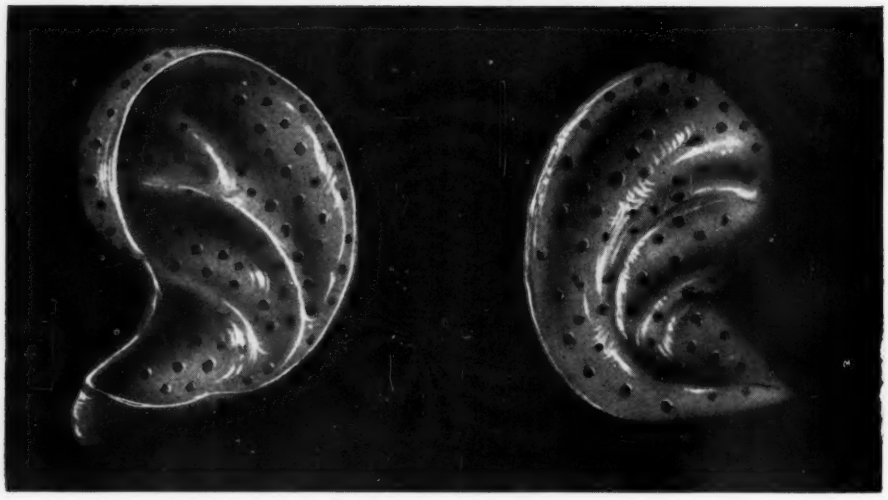
They restore form but do not have normal resilience and by their thickness tend to narrow the nasal airways. Solid cartilage grafts, when used in ear reconstructions, are much more objectionable. They rarely can be made to approximate more than grossly the convolutions of the external ear, and are thick and heavy. The fact that cadaver ear cartilage and living maternal ear cartilage grafts have been resorted to by some surgeons is sufficient evidence that the results in reconstruction of the ear are far from satisfactory. The failure of attempts to restore the ear is due in large part to the inability to reproduce a skeletal framework which has exact form, thinness, and elasticity.

While it might be possible to cast these thin cartilage grafts in situ between two layers of skin or between skin and mucosa, this would still involve the accurate distribution of the particles in regard to

thickness and the accurate retention of complicated forms while the grafts healed. After considering the difficulties which might be encountered it seemed more simple to attempt to produce thin, complicated cartilage grafts by precasting the particles in a form. The graft obtained could then be inserted in the same manner as a solid carved graft.



A.



B.

Fig. 8.—*A*, Photograph of fenestrated metal form of ticonium made from wax model. *B*, A drawing of the metal form which shows the contour more clearly than photographs.

We have not used this method as yet for any other purpose than the reconstruction of ears. However, the method could be used for any type of cartilage graft.

Method.—

1. A wax model of the desired part is made (Fig. 7).

2. A metal shell is then made from the wax model (Fig. 8). (The metal should be nonirritant to tissues. The metal shell illustrated was made of Ticonium.*) It is perforated so that capillaries and fibroplasts can enter.

3. Autogenous costal cartilage is removed and chopped into fine pieces. The form is snugly filled with cartilage particles and buried in the subcutaneous tissues of the abdominal wall.

4. After three to four months the form is removed and opened. The cartilage particles will have adhered to one another in an exact replica of the original wax model (Fig. 9).

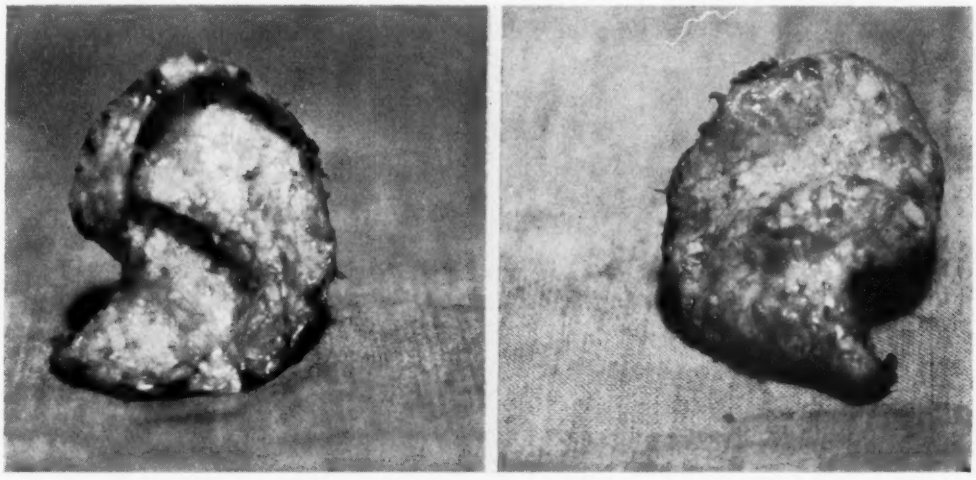


Fig. 9.—Precast cartilage graft on its removal from metal form. This was removed from the form three months after the form filled with cartilage particles was implanted in the abdominal subcutaneous tissues.

5. The graft thus obtained is inserted under the skin in the desired location. The skin is held in contact with the graft by a latex mold until adherent (Fig. 10).

The following case report illustrates the precasting of an auricular cartilage. This case is not entirely completed, although it has pro-

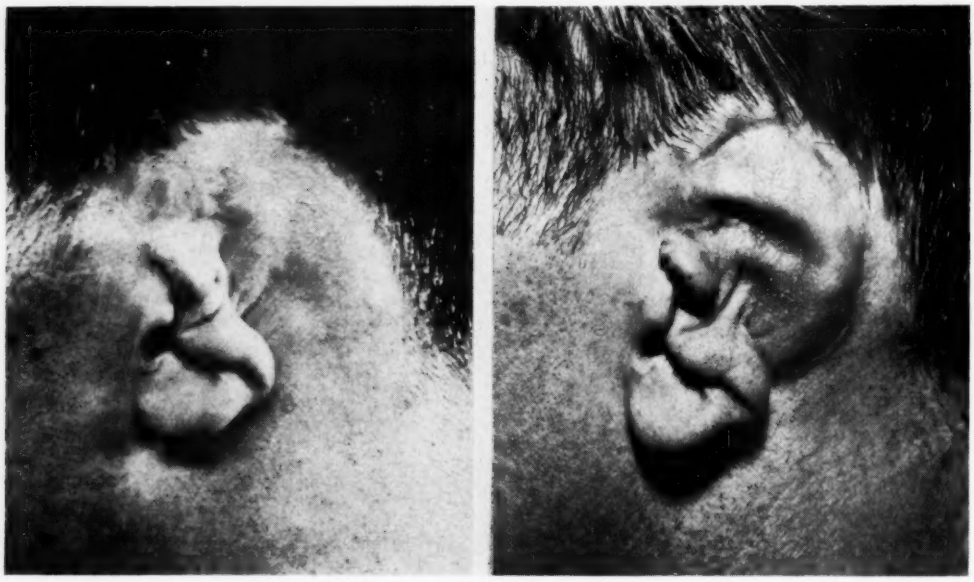
*I wish to express my sincere thanks and appreciation to Mr. Joseph Temkin of the Standard Dental Laboratories, Rochester, N. Y., and to Ticonium, 413 N. Pearl Street, Albany, N. Y., for their interest in this problem. The procedure used in making the metal ear shell was described by them as follows:

"The castings were made with our No. 25 alloy which is somewhat higher fusing than the No. 70 ordinarily used for dentures. This made it impossible to use the regular investment materials and a special high heat investment was employed.

"The procedure was as follows: The wax pattern of the ear which the doctor submitted was flasked and cast. This casting was then polished. Just before the last polishing operation it was mounted in plasticene so that impressions could be taken, first of the back and then of the front surfaces. Stone dies were first run up in these impressions and then working investment models were run up. Twenty-eight gauge wax sheet was cut into strips and adapted on the stone dies, then transferred to the working investment model and sealed down. The separate shells for the front and rear surfaces were thus formed. Care had to be taken that the edges of both pieces would match so that the two castings would fit together to form the hollow shell the doctor wanted.

"The complexity of the ear structure makes adaption of the wax strips difficult and considerable skill is required in this part of the operation."

gressed to the point where the ear has been brought out from the head. The graft has retained its form and gives the promise of being superior to the usual attempt at reconstruction of the ear. This case will be reported shortly in its entirety.



A. *B.*

Fig. 10.—*A*, The appearance of the ear to be restored. *B*, The precast auricular cartilage graft was inserted under a delayed flap three months before this photograph. The rim of the ear is just below and under the hairline. The line of the antihelix stands out sharply.

CASE REPORT

A. T. (S. M. H., No. 199375), a 25-year-old married white man, first consulted me in December, 1942, regarding a deformity of the left ear. He had lost all of the ear, except the lobe, in an auto accident twelve years before. At that time an unsuccessful attempt had been made to reconstruct the missing part.

The ear when I first saw the patient was as illustrated in Fig. 10 *A*. The cartilaginous superior portion of the ear was absent. The lobe was normal. The meatus was covered by a small roll of scarred skin which the patient stated was the net result of the previous attempt at reconstruction. This caused diminished hearing on the left side.

The patient stated that he had worn an artificial ear for a short period but that the inconvenience was so great that he preferred to go without it. He wanted the ear reconstructed if there was a reasonable prospect of success. The procedure was outlined for him and he decided to take the chance.

Plans for the reconstruction were made prior to hospital admission. A complete plaster cast of the head was made. The missing ear was modeled on this in plasticene. This was modeled to match the normal ear as closely as our ability allowed. A cadaver ear cartilage was then selected which corresponded in size and configuration to the ear to be reconstructed. A plaster cast of this cartilage was made in three sections and a wax model of the ear cartilage was obtained. (Fig. 7.)

This model was then taken to a sympathetic dental laboratory and the problem explained. After several trials a metal fenestrated form was made of ticonium which was acceptable (Fig. 8).

The patient was then admitted to the hospital. On May 1, 1943, the first stage of the reconstruction was carried out. Under general anesthesia a piece of costal cartilage about 2 inches long and ¼ inch wide was removed from the right side. The cartilage was chopped into particles about 1/16 inch square. A small amount of cartilage was grafted into still finer particles on an ordinary kitchen vegetable grater. The ticonium shell was packed with cartilage particles and the two halves held together with silk ties around the periphery. An incision about 2 inches long was made over the lateral border of the right rectus at about its mid-point. A pocket was made by blunt dissection between subcutaneous tissues and rectus fascia. The cartilage-filled metal shell was buried in the pocket so that no part of it lay underneath the incision through which it was introduced. The wound was closed with silk and a snug compression dressing applied over the form. A flap, the shape of an ear, was elevated in the left mastoid region and delayed.

The patient did well, no serum collected about the form, the wounds healed per primam, and he was discharged from the hospital on the seventh postoperative day. The patient returned to work in about two weeks and follow-up was continued at infrequent intervals in the office. On July 7, 1943, two months after the insertion of the form, the flap in the mastoid region was further elevated and delayed under local anesthesia without hospitalization.

On Aug. 10, 1943, the patient was readmitted to the hospital and the form buried in the abdominal wall removed under general anesthesia. The tissues were so firmly adherent to the form that it had to be removed by sharp dissection. It was covered by a thin layer of young, slightly yellow fibrous tissue. The form was opened and the cartilage removed without great difficulty. A perfect replica of an ear cartilage was obtained (Fig. 9). The particles could still be seen on its surface and the cartilage was somewhat soft. It was resilient, could be bent to an angle of 45 to 60 degrees, and would slowly return to its original shape. From the appearance of the graft and a comparison with similar grafts obtained over longer periods of time in dogs, it would probably have been better to have allowed the form to remain buried for six months or longer rather than the three-month period allowed. The flap in the mastoid region was elevated and the cartilage form inserted. It was found that in order to do this the scalp had to be undermined about ½ inch posterior to the flap and the rim of the cartilage allowed to rest under hair-bearing skin. In retrospect it would probably have been better to have supplied a little excess skin at the periphery of the hairless mastoid skin prior to insertion of the graft. This would have allowed the graft to rest under hairless skin and moreover would have lessened the chance of distortion of the graft due to the tightness of the skin over it. The incisions were closed and a latex form strapped in place to maintain the mastoid skin in close approximation to the graft.

There were no complications postoperatively. There was quite pronounced edema of the skin over the graft and a small amount of serous fluid accumulation. The edema subsided slowly and as it did the outline of the ear became evident (Fig. 10).

On Nov. 4, 1943, about three months after insertion of the precast cartilage graft, the graft was dissected free from the head leaving the skin attached anteriorly and the cartilage covered by a thin layer of soft tissue posteriorly. The posterior surface of the ear and the mastoid area was covered with a free full-thickness skin graft. The graft took incompletely on the posterior aspect of the ear, undoubtedly due to evident poor circulation at the periphery of the flap of skin and attached cartilage; the mastoid skin graft took in its entirety. However, in spite of this only a few particles of cartilage were lost on the rim of the ear superiorly. The wound granulated and was covered with a split-thickness

graft. February, 1944, the ear was in this condition; it stood out from the head and had good convolutions; it was almost as thin as the normal ear. The cartilage graft in the six months it had been in place had shown no signs of disintegrating or losing shape. Its long-term fate will be reported.

SUMMARY

Cast Cartilage Grafts.—The best material for use in the restoration of lost parts of the facial skeleton is autogenous costal cartilage. It has long been used as solid grafts carved to the desired shape. This method has disadvantages. Among these are the lack of large enough pieces of cartilage to restore large losses, the inability to model the grafts to exact shape in the short time available at operation, the difficulty of fixation, and the tendency of solid cartilage grafts to subsequently warp.

Previously reported animal experiments show that small bits of cartilage buried together in the subcutaneous tissues adhere by fibrous tissue. In this way grafts of cartilage having the physical properties of elastic fibrocartilage can be produced.

This method has been used in restoring lost facial contour. The fine details of facial form can be restored by implanting a mass of cartilage particles subcutaneously and maintaining them in exact shape as they heal together by appropriately constructed latex forms. The implanted cartilage is thus cast in situ in an exact predetermined replica of the part desired.

Precast Cartilage Grafts.—In certain locations thin, elastic, cartilage grafts of complicated contour are desirable. In reproducing the cartilage, for example, of an ear, even greater difficulties are encountered if an attempt is made to use a solid carved graft. Cartilage of sufficient size is not available and the carving of the complicated contour is time consuming and difficult. An exact replica of an ear cartilage can be reproduced by filling a fenestrated metal form with finely divided cartilage and burying this in the subcutaneous tissues. In three months' time the particles are adherent and can be removed from the form as a thin, elastic sheet of cartilage which has the exact contour of the detailed configuration of an ear. This replica of ear cartilage can be used as the skeletal support for reconstruction of the ear, will retain its form and shape, and when covered with mastoid skin closely simulates a normal ear.

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SURGICAL TREATMENT OF LONG-STANDING DEEP PHLEBITIS OF THE LEG

A Preliminary Report*

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TREATMENT of the incompetent or insufficient veins of the lower extremities has occupied the enthusiasm of the profession at intervals. With each wave of enthusiasm a modicum of progress has been made. Much of the recent progress has centered upon the recognition and acceptance of two etiologically different forms of venous thrombosis, the metastatic tendencies of these, and a rationale of treatment. To most, the terms thrombophlebitis and phlebothrombosis[1] are now well known. Every physician has encountered the patient who has had a pulmonary embolus. Its relationship to phlebothrombosis is now recognized and femoral vein ligation is employed, as a preventative measure, with excellent and well-authenticated results.

The patient with the acute suppurative and nonsuppurative postoperative, postparturient, or post-traumatic phlebitis has likewise received much attention and many forms of treatment.[2] Perhaps the most successfully treated are those in whom the superficial venous systems of the legs have been involved. Success in varying degrees has been obtained by treatment ranging from the ultraconservative heat, rest, and elevation to lumbar sympathetic block,[3] iontophoresis,[4] anticoagulant therapy,[5] and surgical ligation.[6]

A large portion of the patients seen in many vascular clinics over the country fall into the less fortunate group of "chronics." In these patients swelling of the leg or legs has persisted over a long period of time. The skin has become thickened, infiltrated, and pigmented, the leg is heavy and painful, especially with long standing and the later sequelae of dermatoses, and indurations and ulceration are frequently present. To this group of patients we wish to draw particular attention.

If one looks back over the various methods of treatment of the diseases of veins of the lower extremities he is impressed with the fact that the progress of treatment has far outstripped our actual knowledge of

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the physiology and mechanics and even the anatomy of this portion of the vascular tree. The earliest forms of attack were clearly definitive and were directed at the removal or obliteration of the large, unsightly, troublesome superficial varicosities of the leg. Celsus[7] exposed these veins with various incisions, "separated from each other by the breadth of four fingers," and destroyed them with the cautery or cut them at various points and tore out the segments between. Paulus of Aegina[7] (about 660 A.D.) appears to have opened the trunk of the saphenous vein especially for the purpose of removing a thrombus and to have ligated the vein following this removal. Marcus Aurelius Severinus[7] also advised excision of varices and apparently was familiar with the favorable influence of this procedure on crural ulcers. Ambroïse Paré,[7] although basing his views on a false theoretical foundation as to the direction of the blood flow in the normal saphenous veins, was correct in advising their ligation. Fabricus Hildanus,[7] in 1589, gave an excellent description of a large varix with an associated chronic ulcer treated by him and cured by saphenous ligation.

That the ligation of the saphenous vein fell into some oblivion may be due to the discovery of the circulation. Inasmuch as the venous trunks were only efferent passages for the conduction of the blood and the varicose dilatation was due to congestion, how could ligation of the trunk be of benefit? It is said that John Hunter,[8] in the latter part of the eighteenth century, recommended compression of the vein above a thrombus in order to produce adhesive occlusion of the vessel above an obstruction. At the end of this century Everard Home[7] again took up the idea of saphenous ligation and ligated the trunk of the saphenous just below the knee joint in twelve cases in order to heal ulcers of the leg and bring about a regression in the varicosities. Henry Lee,[8] in 1865, cured several cases of purulent thrombophlebitis of superficial veins of the extremities by ligation of the veins above the affected areas.

Kraussold,[8] in 1878, was apparently the first to resort to femoral vein ligation. He was able to cure pyemia following infection of an amputation wound by ligation of the femoral vein with resection of a portion of this venous trunk. Gluck,[9] in 1896, reported a postabortion septic thrombophlebitis of the long saphenous vein cured by ligation of the common femoral vein. Müller,[9] in 1909, reported a similar case.

In this country Griess,[8] in 1913, was probably the first to resect the femoral vein for septic thrombosis.

Since this time many authors have reported femoral ligation upon various indications, most of which are acute processes such as suppurative thrombophlebitis, direct trauma to the vein, and phlebothrombosis. Homans[6] stated that "it is reasonable to assume that an old, sclerosed, canalized femoral or external iliac vein is better divided." He further states that he has never performed division of such a vein for back pressure alone but "I am sure that the procedure—

barring the risk of any such operation in patients of middle age or beyond—will always do good and never harm.''

Progression in our clinical knowledge of the response of patients to venous ligation has been followed apace by higher and higher ligation of the venous tree. Ligation or excision of the pelvic veins in the treatment of suppurative thrombophlebitis of puerperal origin was advocated by Bumm and Trendelenburg and others.[8] In 1921, Martens[9] reported eleven gynecologic cases of thrombophlebitis in which ligation of the ovarian vein as well as that of the internal or common iliac vein was done. In two cases the inferior vena cava was successfully ligated. Caval ligation is still done with some temerity but with increasing frequency.

The venous system in the lower extremity, like that in other portions of the body, shows numerous variations from the so-called normal. In general, venous blood is returned, all or in part, through five groups of vessels:[10] (1) deep veins of the leg; (2) superficial veins of the leg emptying into the femoral; (3) superficial veins emptying into the popliteal vein; (4) superficial and deep veins emptying into the internal iliac veins; and, (5) the communicating veins.

Much of our recent knowledge of the veins of the legs is derived from venographic studies after the injection of an opaque medium. The normal venous tree as described by Gunnar Bauer[11] and interpreted from almost 100 venographic studies is as follows:

Femoral Vein: The femoral vein appears as a thick cord ascending in a slightly medial direction from a point a little above the knee joint. Malformations or aplasia are rare. Bulbous thickenings appearing in the course of the vein indicate the presence of valves.

Popliteal Vein: The popliteal vein is considerably less uniform than the femoral, being subject to wide anatomic variation. Its length is highly variable depending upon whether the tibial veins unite at a high or low level. The vein is double in a large number of cases.

Anterior Tibial Vein: For its whole course, the anterior tibial vein is usually seen beginning in the retromalleolar area and projected free in the space between the tibial and fibular shadows. Ordinarily this vein is double for the whole of its length, or at any rate along its lower course; sometimes it is multiple and appears as a large group of thick trunks.

Posterior Tibial Vein: The posterior tibial vein, because of its poor anastomoses with the small saphenous vein, the vein usually used for opaque injections, is less well known in the lower one-third of the leg. In its upper two-thirds the vein is practically always doubled, passing in a lateral direction against the tibial shadow toward the popliteal vein.

Muscle Veins: The most constant of the muscle veins are the lateral and medial sural veins, which are always double and bring blood from the two bellies of the gastrocnemius muscle. They empty into the popliteal vein almost exactly at the knee joint gap.

Peroneal Vein: The peroneal is a very inconstant vein and its caliber is small. Occasionally it can be seen coming from a lateral direction, crossing the shadow of the anterior tibial vein and opening into the upper end of the posterior tibial vein.

Superficial Cutaneous Veins: The greater and lesser saphenous system, while less constant than most of the deep veins, is quite well known and its branches are well described in most anatomy texts.

The number and location of valves vary in different veins and for the same vein in different individuals. One relationship which is fairly constant for valves is their association with tributaries. A valve is almost constantly found just below the ostium of a moderate-sized tributary. Hesse and Schaack[10] found the valve in the femoral vein just above the entrance of the long saphenous vein present in 77 per cent of cases. Eger and Casper,[12] in a series of thirty-eight cadavers, studied the valvular distribution in the external iliac and femoral veins proximal to the orifice of the great saphenous and found that in no vein was more than one valve present and that valves were bilaterally absent in 7.9 per cent of the cadavers and unilaterally absent in 28.9 per cent. Unilateral absence was almost twice as frequent on the left side as on the right. There are no valves present in the vena cava or common iliac veins.

Like the arterial adventitia, the outer coat of the large veins is supplied with a rich ramification of sympathetic nerve fibers. Consequently, as in the case of arterial thrombosis, the inflammation of the outer mural layers in venous thrombosis is attended by irritation of these sympathetic elements. Further, as is quite natural, the adventitia of the adjoining artery is also affected by the periphlebitic changes, and the sympathetic nerve fibers here are also irritated to a great extent. Thrombosis of the femoral vein is therefore attended by a universal vasospasm in the leg.

In viewing the patient with a long-standing, deep, chronic thrombophlebitis, one is impressed by at least three possible factors contributing to the visible effects of the disease: (1) thickening and tortuosity of the walls of a vein and final destruction from scarring of a part or all of its valves; (2) vasospasm, resulting in a cold, cyanotic extremity; and, (3) often a brawny edema suggesting a variable element of lymphatic obstruction.

Obviously the femoral or iliac veins, once thrombosed, lose the function of their valves so that in the erect position blood must pour down a valveless vein and returning blood must take, in part, collateral valved pathways. When the phlebitic process is extensive even these must be, in part, incompetent.

Homans[6] described three types of vasospasm associated with a femoroiliac thrombophlebitis: (1) The diffuse peripheral type, thought to occur principally in the venules, and believed to be an important cause of the edema of phlegmasia alba dolens; (2) that represented by a sudden constriction of the great artery accompanying the thrombosed vein; and, (3) the late, diffuse peripheral spasm, related to the early acute

type, which may remain for years after the initial phlebitic attack has subsided.

Under the clinical circumstances of venous block, or increased venous pressure, all of the factors making for increased lymph formation—in the sense of added capillary filtration—will operate; but lymph will not flow rapidly from the part unless such measures as active or passive motion or posture are taken which assure movement of fluid in the lymph capillaries.[13]

The solution of the problem presented in the light of these factors then depends upon the release of vasospasm and the introduction of a procedure to replace the destroyed valvular system in the femoral vein. We have attempted to solve these two problems by ligation of a portion of the femoroiliac system. We have not had satisfactory permanent results with repeated lumbar sympathetic novocain blocks, nor have we been in any way fully convinced of the importance of permanent lymphatic obstruction in any of our patients.

Up to the time of this writing we have performed femoral ligations upon twenty-one patients for chronic deep thrombophlebitis. In one of these patients subsequent ligation of the vena cava was necessary. As yet no ligations of the iliac veins alone have been carried out for this disease. Whenever superficial varicosities were present in these patients, ligation of the varicosities was done before the decision to institute femoral ligation was made. No injection therapy was used in conjunction with the ligations. In those patients in whom ulcerations have persisted, when swelling and pain have not been relieved, or in whom venograms have demonstrated block or varicosities in the deep venous system, the femoral or caval systems have been ligated. Venography was not carried out on our patients unless symptoms persisted after the indicated ligations had been carried out in the superficial systems so that ligation of the deep systems was never based upon venographic evidence of the disease alone. We have attempted to limit ligations to individuals of less than 55 years of age, although two patients were older than this empirical age limit at the time of ligation. No patient with demonstrable advanced arterial disease has been accepted for this procedure.

At the time of this communication, it has been five months since the first patient had femoral ligation for chronic deep thrombophlebitis. In no instance has demonstrable harm been done to any patient.

A very striking and immediate relief of pain about an ulcer occurred in the majority of patients. Several patients expressed relief of pain as soon as the ligature was tied about the vein. Almost all had some increased swelling of the leg for at least the first forty-eight hours following ligation. Ligation has been done above the level of the profunda femoris in those patients with a history or clinical evidence of swelling above the knee, and in these patients the immediate increased swelling

has included the thigh. In no case has lumbar sympathetic injection accompanied the operative procedure.

We have observed very interesting, and in some instances very troublesome, sequelae. One of the most troublesome has been the frequent appearance of superficial varices in the lower leg several weeks following femoral ligation. In several of our patients progressive healing of an ulcer has occurred, healing has then ceased, and the ulcer has enlarged or reappeared after healing has occurred, with the appearance of superficial varices. Our method has been to ligate these veins as quickly as they appear. Six of the twenty-one patients have required subsequent serial ligation of superficial veins which have appeared since ligation of the femoral vein.

A second complication which has produced considerable concern is the persistent or increased swelling of the leg and thigh after operation. It has been our policy to mobilize these patients within forty-eight hours after ligation. In seven patients this has been followed by persistent or increased swelling. In four patients this has been controlled by a short period, one to two weeks, of bed rest. The other patients in this group have been unable to accept this form of treatment.

One patient returned to the hospital for incision and drainage of an abdominal abscess (not related to ligation) four months after the ligation of the femoral vein for a suppurative thrombophlebitis superimposed upon a long-standing chronic thrombophlebitis with ulceration. Forty-eight hours following this operation symptoms of an acute arterial embolism in the popliteal artery appeared. No relief was obtained by repeated lumbar sympathetic novocain blocks and amputation was done after demarcation had occurred. We do not feel that the femoral ligation, done four months before, was in any way a contributory factor in this patient. The leg had been completely asymptomatic, without swelling or recurrent ulceration, in the interim.

A second patient, following femoral ligation, developed increased, bilateral leg edema associated with dilated thoracoabdominal veins that were more marked on the side of the femoral ligation. Ligation of the inferior vena cava was performed subsequently and the bilateral edema has subsided although the patient is yet too early in his convalescence to show convincing evidence of improvement. Obviously this patient's first ligation was done distal rather than proximal to the level of his disease.

Fourteen of the twenty-one patients treated in this manner have had chronic leg ulcers which have been present continuously or intermittently for from three months to thirty-five years. In all fourteen patients ulcers were present at the time femoral ligation was done. A striking response, following ligation, has been the relief of pain in the majority of the patients. In four patients complete healing of the ulcer or ulcers has occurred, while in another four healing is progressing

at a satisfactory rate. In four patients no noteworthy change has occurred in the size of the ulcer and in three patients the ligation has been done too recently for observable change to appear. In one patient in whom no noticeable change has occurred in ulcer size, the ulcer has been recently excised and the area grafted. This patient's swelling has subsided and the leg and thigh are no longer painful. The ulcer itself remained persistently painful and was therefore excised.

SUMMARY

In twenty-one patients femoral vein ligation has been done for chronic deep thrombophlebitis. In one patient a subsequent ligation of the vena cava was necessary. The first ligation in this series of patients was done in September, 1943.

Sixteen of the twenty-one patients so treated have shown definite improvement. In no patient has definite harm been done.

Those patients with clinical and venographic evidence of deep thrombophlebitis, whose symptoms have failed to improve following high and low ligations of existing varicosities in the superficial venous systems, have been advised to have ligation of the femoral vein. No ligations have been done in patients with advanced arterial disease.

Six of the twenty-one patients have developed superficial varices following femoral ligation and these have been ligated as they appeared.

In seven patients persistent or increased swelling of the leg has occurred following ligation. This swelling has been controlled in four patients by a short period of bed rest. In three patients a period of bed rest has not been practicable.

Fourteen patients have had chronic leg ulcers at the time of femoral vein ligation. Following ligation, complete healing of the ulcers has taken place in four patients, healing is progressing satisfactorily and steadily in four other patients, while in an additional four patients no change in the size of the leg ulcers has occurred. In three patients operation has been done too recently for demonstrable change to be noted.

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SWELLING OF THE UPPER EXTREMITY FOLLOWING RADICAL MASTECTOMY

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INTRODUCTION

AFTER having seen a patient who developed swelling of the arm two and one-half years after radical mastectomy, we became interested in trying to determine the cause of such swelling.

We have examined 100 patients subjected to radical mastectomy, the period of time elapsing since operation ranging from six months to eleven years. These were not consecutive cases and were selected on the basis that they were available for follow-up examination during 1943. The arms of these patients were measured, the presence or absence of swelling noted, and data collected relating the swelling to grafting, infection, recurrence, and roentgenotherapy.

HISTORICAL

Matas defined elephantiasis as "a progressive histopathological state characterized by chronic inflammatory fibrosis and hyperplasia of the dermal and hypodermal tissues, which is preceded by and associated with venous and lymphatic stasis." In this series there was no instance in which the clinical findings were compatible with this definition.

Of the seventy patients who had some degree of swelling, the axillary vein had not been ligated nor was it blocked by tumor. Furthermore, venous engorgement and superficial venous collateral circulation was noted in no instance. We shall refer to this condition simply as swelling of the arm.

Halsted stated that "although blocking of the lymphatics, and occasionally also of the veins, was the underlying factor, infection played a conspicuous part in the determination of the amount of swelling and the time of its manifestation." He described one patient who, three years and three months after radical mastectomy, developed lymphangitis of the arm. Swelling began simultaneously, was extreme in a few days, then decreased but failed to disappear after the infection subsided. Another case was recorded in which the patient had slight wound infection and during the succeeding ten years had one to four attacks yearly of redness and swelling of the arm. Halsted found that swelling

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occurred less frequently after he abandoned the incision down the arm and started reconstructing a high axilla which eliminated dead space below the clavicle and permitted free motion of the arm.

Halsted and Reichert amputated the hind legs of dogs leaving only the femur and the media and intima of the femoral artery and vein intact, and carefully reapproximated the tissues. They demonstrated regeneration of the superficial and deep lymphatics and were unable to produce permanent edema by injecting India ink, or to effect true infection in the animal's leg.

Reichert stated that he had records of two cases in which the axillary nodes had been excised (one for carcinoma of the breast, the other for carcinoma of the hand) and "in which incipient elephantiasis was present due to repeated attacks of malaise, fever, and vomiting, associated with pain and swelling of the affected extremity following the eating of shellfish."

ANALYSIS OF CASES AND DISCUSSION

Measurements of circumference were arbitrarily made 10 cm. above the tip of the olecranon, at its tip, and 10 cm. below it. In several normal subjects who were measured, the greatest difference in circumference of the arms of right-handed individuals was found to be 1 cm. or less. Except in very thin patients the presence of swelling is not detectable if the difference between the arms is less than 3 cm.; and in two instances, in which the difference was 4.5 cm., swelling had not been noted. Thus, it is apparent that a significant degree of swelling may exist without recognition unless measurements are made.

An analysis of the cases studied is shown in Table I. The percentage of swelling was slightly lower in those cases in which primary grafting was done (65 per cent) than in those without grafting (83 per cent). The percentage of marked swelling—6 cm. or more—was approximately the same, being 11 per cent for those with graft and 10 per cent for those without.

It seems that axillary metastasis does not contribute to swelling, for 66 per cent of those with axillary metastasis had measurable swelling, as compared with 71 per cent of those without involvement of the nodes.

In 26 per cent of the patients who received roentgenotherapy, there occurred no instance of swelling and the same is true of 37 per cent of those not so treated. Of the remaining 74 per cent who were irradiated and who developed swelling, eleven patients, or 17 per cent, had marked swelling. On the contrary, in cases not given roentgenotherapy, not one developed marked swelling.

The term infection, as used here, applies not only to wound infection, but to any infection in areas drained by the lymphatics of the axilla in question. "Early infection" is used to denote infection before the wound was healed. "Late infection" indicates infection arising after

TABLE I

RELATION OF SWELLING OF ARM TO GRAFTING, AXILLARY METASTASES, ROENTGENOTHERAPY, INFECTION, LOCAL RECURRENCE, AND WOUND HEALING

	NUMBER OF CASES	PATIENTS WITH NO SWELLING	PATIENTS WITH SWELLING[7]		
			UNDER 3 CM.	3 CM. OR MORE BUT NOT 6 CM	6 CM. OR MORE
Total number of patients examined	100[1]	30	26	33	11
Patients with primary graft	71[1]	25 (35%)	16 (23%)	22 (31%)	8 (11%)
Patients without primary graft	29	5 (17%)	10 (35%)	11 (38%)	3 (10%)
Patients with axillary metastases	32[2]	11 (34%)	8 (24%)	11 (34%)	2 (6%)
Patients without axillary metastases	69[3]	20 (29%)	18 (26%)	22 (32%)	9 (13%)
Roentgenotherapy administered	66[2]	17 (26%)	15 (23%)	22 (33%)	11 (17%)
No roentgenotherapy	35	13 (37%)	11 (31%)	11 (31%)	0
Patients with infection					
Early infection	18[8]	3 (17%)	6 (33%)	4 (22%)	5 (28%)[8]
Late infection	25	0	8 (32%)	9 (39%)	8 (32%)
Patients without infection	59	27 (46%)	12 (20%)	20 (34%)	0
Patients with skin recurrence	5[4]	2	1	2	
Healing per primam	14	6 (43%)	4 (28%)	1 (7%)	3 (22%)[5]
Healing by secondary intention	86[6]	24 (28%)	22 (25%)	32 (37%)	8 (9%)

[1]Three patients had bilateral mastectomies.

[2]One patient had two radical mastectomies (only thirty-two patients with axillary metastases; sixty-five patients receiving x-ray therapy).

[3]One patient had bilateral mastectomies with metastases in one axilla only.

[4]Two of the five patients had grafts, three did not.

[5]Two patients had late infections and one had chronic paronychia at the time of operation.

[6]All patients who had 3 cm. swelling or more did not heal per primam except four, three of whom were noted.[5]

[7]Measurements listed here are the greatest difference in circumference of two arms.

[8]Two patients had early and late infection.

healing of the mastectomy wound. Examples of early infection are sloughing of the graft or skin flap with associated purulent discharge, axillary abscess, and lymphangitis. Roentgen-ray dermatitis, paronychia, burns of the hand, and dog bites are examples of late infection. There were only six instances of wound infections; one with erysipelas of the wound, one with cellulitis of the tissues surrounding the wound, and four with frank pus from sloughing skin flaps. Close questioning of the patients revealed that forty-one had some type of infection at some time between operation and final follow-up examination. Marked swelling never developed in patients who did not have a record of infection. Only three patients with early infection escaped swelling and all with late infection developed it; furthermore, all eleven patients with marked swelling had either early or late infection or both.

The statement has appeared in the literature and the belief is common in the lay mind that swelling of the arm indicates recurrence of carcinoma. In this series there were only five cases of local recurrence, three with slight or moderate swelling and two with no swelling. Ax-

illary recurrence did not occur. Thus, sixty-seven patients showed some degree of swelling without local or axillary recurrence.

Healing by "primary intention" is a term which probably cannot fairly be applied when primary skin grafting is done. In addition, our classification was rigid and if there was even one area of granulation tissue, such a case was listed as closed by secondary intention. Consequently, healing by primary intention could be said to have occurred in only 14 per cent of patients. Forty-three per cent of those healing per primam had no swelling, as contrasted with 28 per cent of those healing by secondary intention. Of the three patients in whom healing was per primam and who developed marked swelling, two had late infections and one had a paronchyia at the time of operation.

Primary skin grafting appeared to have little bearing on the development of swelling (see Table II). Swelling was present in all of the twenty-nine patients who had both roentgenotherapy and infection. Similarly, all who developed marked swelling had both roentgenotherapy and infection.

Table III gives an analysis of the eleven patients who developed marked swelling of the arms, that is of 6 cm. or more difference in circumference of the arms. The site of measurement which gave the maximum figure was usually above the olecranon, but was occasionally at the olecranon or below it. All patients except two had primary grafts. The interval between operation and marked swelling ranged from one month to two and one-half years. Eight patients had irritation of the skin from roentgen ray ranging from marked dermatitis with serous exudation to frank ulceration with purulent discharge. In addition, one had a wound infection two months after operation, one had partial sloughing of a flap with infection, and one had psoriasis of the elbow

TABLE II

RELATION OF SWELLING OF ARM, IN PATIENTS WITH AND WITHOUT PRIMARY GRAFT, TO INFECTION AND ROENTGENOGRAPHY

		NUMBER OF CASES	NUMBER OF CASES WITHOUT SWELLING	AMOUNT OF SWELLING		
				LESS THAN 3 CM.	3 OR MORE BUT NOT 6 CM.	6 CM. OR MORE
Without infection, Without x-ray	with graft	16 (22%)	8 (11%)	4 (6%)	4 (6%)	0
	without graft	7 (24%)	2 (7%)	2 (7%)	3 (10%)	0
With infection, Without x-ray	with graft	8 (11%)	2 (3%)	3 (4%)	3 (4%)	0
	without graft	4 (14%)	1 (3%)	2 (7%)	1 (3%)	0
Without infection, With x-ray	with graft	25 (35%)	15 (21%)	3 (4%)	7 (10%)	0
	without graft	11 (38%)	2 (7%)	3 (10%)	6 (20%)	0
With infection, With x-ray	with graft	22 (31%)	0	6 (8%)	8 (13%)	8 (13%)
	without graft	7 (24%)	0	3 (10%)	1 (3%)	3 (10%)
	Total	100				

before and after operation. Of the three patients who did not have roentgen-ray dermatitis, one had a chronic paronychia at the time of operation, one had a wound infection three weeks after operation, and one had a dog bite on the hand two and one-half years after operation. The time interval between the occurrence of infection and the appearance of swelling ranged from two weeks to four months. This recorded interval probably is much longer than the true one as some patients were not followed at intervals shorter than three months and the exact date of swelling noted on the records is often later than that of its actual appearance. The only other explanation of the lag between infection and swelling is that late fibrosis may result in lymphatic blocking. In patients in whom radical mastectomy with the usual wide dissection of tissues of the axilla and surrounding area has been done, a fine balance exists between the afferent and efferent vessels. Whether or not swelling of the arm develops appears to depend upon whether the remaining lymphatics of the arm are sufficient to drain the arm of lymph. Infection may immediately cause destruction or blocking of lymphatics with concurrent swelling. In other instances swelling may not develop until later when postinfectional fibrosis has blocked even more lymphatics.

As far as could be determined, roentgenotherapy per se did not tend to cause swelling unless it was associated with dermatitis, when the swelling was apparently attributable to it.

Of the seventy patients who had swelling, only eleven had differences of circumference of the arms of 6 cm. or more. The function of the arm was good in ten of these and fair in the eleventh. Of the fifty-nine who had lesser degrees of swelling, forty-nine had good function and ten had fair function (see Table IV). Swelling did not incapacitate any patient but caused only such symptoms as heavy feeling, slight loss of strength, and occasional aching. All patients in this series were mentally adjusted to the presence of swelling.

TREATMENT

After swelling of the arm has developed, the treatment is unsatisfactory. Conservative measures such as suspending the arm at night, gentle massage, and rest are rarely of lasting benefit. Some of the patients in this series thought that use of the arm increased the swelling, but a few stated that the swelling diminished after use. Operative measures such as the Kondoleon operation, ligation of the axillary vein, as advocated by Buxton and associated for deep thrombophlebitis, or fixation of the arm to the chest wall (Standard), were not justified in this series.

PREVENTION

Every effort should be made to secure primary wound healing and to prevent the collection of serum under the flaps. All possible precau-

TABLE III

HISTORY NUMBER	GRAFT	HEALING TIME	INTERVAL BETWEEN OPERATION AND SWELLING	DESCRIPTION OF INFECTION	TIME FOR INFECTION TO HEAL	INTERVAL FROM HEALING OF INFECTION TO APPEARANCE OF EDEMA	INTERVAL BETWEEN APPEARANCE OF INFECTION AND SWELLING	MEASUREMENTS (IN CM.)‡ RT.	LT.	MAXIMUM DIFFERENCE (IN CM.)	INTERVAL FROM OPERATION TO EXAMINATION (IN YR.)
2248	No	12 wk.	4 mo.	(1) Partial slough of medial flap followed by purulent discharge	(1) 11 wk.	5 wk.	(1) 4 mo.	34.5 29 27.6	28.2 24.2 22.5	6.3	3½
				(2) Marked skin reaction during x-ray therapy	(2) 6 wk.	1 wk.	(2) 5 wk.				
116899*	No	8 wk.	7 mo.	Marked skin reaction two wk. after completion of x-ray therapy	6 wk.	10 wk.	4 mo.	35 32 30	28 25 26	7	2
179674	Yes	10 wk.	5 mo.	(1) Psoriasis of elbow before and after operation	(1) ?	1 mo.	(1) 6 mo. P.O.	36.5 30	28 26	8.5	5½
				(2) Seropurulent discharge from axilla 3 days after completion of x-ray therapy	(2) 2 mo.	1 mo.	(2) 3 mo.	28.5	24		
181023	Yes	5 wk	3 wk. (slight) 2½ yr. (marked)	Dog bite on hand	Few days	4 mo.	4 mo.	36 32.2 32.6	27.4 24.8 23.8	9.2	6

186657	No	per primam	5 mo.	X-ray dermatitis with ulceration	4 wk.	4 wk.	2 mo.	26 25 22	33.5 32 29	7.5	5½
199773	Yes	12 wk	6 mo.	X-ray dermatitis in axilla with erosion, vesiculation, and weeping	2 wk.	10 wk.	3 mo.	29 24.5 20.5	35 29.2 26.3	6	5½
222607	Yes	3 wk.	1 mo.	Chronic paronychia at time of operation, present two yr.	?	?	1 mo.	30.5 29 25	39.5 32 28.5	9.5	3½
252067†	Yes	7 wk.	5 mo.	(1) Marked skin reaction to x-ray (2) Infection under graft 9 mo. after x-ray therapy	(1) 2 wk. (2) 6 mo.	2 wk.	(1) 1 mo. (2) Swelling already present, no increase	34.5 30 28.5	28 23 22	7	3½
276146	Yes	3 wk.	6 mo.	X-ray dermatitis with ulceration			3 mo.	29.3 25.3 23.2	40 36 35	11.8	3
290359	Yes	12 wk.	3½ mo.	(1) Abscess in outer angle of wound; incision and drainage 2 mo. P.O. (2) X-ray dermatitis with vesiculation on graft	(1) 15 days (2) 2 wk.	4 wk. 2 wk.	(1) 1½ mo. (2) 1 mo.	38.5 34.3 33.5	31.7 29.8 29.8	6.8	2½
314577†	Yes	2 mo.	2 mo.	Infection of wound 3 wk. after operation	4 wk.	2 wk.	2 wk.	27.5 24 23	37.4 33 30	9.9	1

*Axillary lymph nodes invaded by carcinoma at time of operation.
†Function good in all patients except in this case in which it was fair.
‡Measurements were taken 10 cm. above olecranon, at olecranon, and 10 cm. below olecranon.

TABLE IV

INFLUENCE OF SWELLING ON FUNCTION OF THE ARM

		FUNCTION		
		GOOD	FAIR	POOR
Total cases with marked swelling	11	10	1	0
Total cases with moderate or little swelling	59	49	10	0
Total cases with swelling	70			

tions should be taken to avoid roentgen-ray dermatitis by discontinuing therapy temporarily, rather than permitting ulceration to occur. Just as patients with diabetes are instructed to care for their feet, these patients should be instructed in the care of the hands and urged to give prompt attention to even minor wounds and infections. It is important to prevent psychic trauma by warning all patients of the possibility of swelling before it occurs and assuring them that it does not mean that cancer has recurred.

SUMMARY

One hundred patients subjected to 103 radical mastectomies have been examined with particular reference to swelling of the arm. The results of the study are summarized in Table V.

TABLE V

SUMMARY OF RESULTS OF THE STUDY

	NUMBER OF CASES	NO SWELLING (PER CENT)	SWELLING (PER CENT)	MARKED SWELLING (PER CENT)
Grafted	71	35	65	11
Not grafted	29	17	83	10
Roentgenotherapy	65	26	74	17
No roentgenotherapy	35	37	63	0
Infection	41	7	93	27
No infection	59	46	54	0
Total	100	30	70	11

The relation of swelling to primary grafting, skin recurrence, axillary metastasis, infection, and roentgenotherapy has been discussed.

Methods of prevention and treatment have been described.

CONCLUSIONS

Primary skin grafting has no influence on the occurrence of swelling of the arm following radical mastectomy.

Swelling of the arm cannot be assumed to signify recurrence of carcinoma.

The presence or absence of metastasis to the axillary nodes at the time of operation has no bearing on the swelling.

In this series of cases by far the greatest factors in the cause of swelling of the arm are infection and roentgen-ray dermatitis

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SIGNIFICANCE OF THE NITROGEN LOSS IN THE EXUDATE FROM SURFACE BURNS

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INTRODUCTION

IT IS recognized that the body loses a certain amount of protein from a burned surface, but since no quantitative figures on this loss are recorded it has been impossible to evaluate its importance.

Blisters begin to appear shortly after a patient has sustained a second degree burn. The loss of protein begins coincidently with the formation of these vesicles. McIver[1] and also Harkins[2] have analyzed the fluid obtained from these vesicles and found it to be somewhat similar to plasma in respect to its protein and electrolyte content. The fluid usually contained 3 to 4 Gm. of protein per 100 c.c. Profuse loss of this plasmalike fluid from the surface of second degree burns ceases after about forty-eight hours, but a considerable amount of exudate continues to accumulate on the dressings until re-epithelization occurs.

Third degree burns do not "weep" significantly during the first forty-eight hours because the burned skin has been so coagulated that it forms a firm leathery insensitive eschar. However, after a few days this eschar softens and begins to slough, allowing copious exudation which persists until skin grafting has been completed.

Our interest in determining the amount of nitrogen which is lost from these burns began when we decided to undertake a study of the alterations in the nitrogen balance of burned patients in relation to variation in diet and to their urinary excretion of cortin, 17-ketosteroids, androgens, estrogens, and gonadotropins. It was apparent that a true nitrogen balance could not be obtained unless the loss of nitrogen from the burned surface could be determined.

The work described in this paper was done, in part, under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Wayne University. It was supported in part by grants from Frederick Stearns & Company and the Theodore A. McGraw Fund for Surgical Research.

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MATERIALS AND METHODS

From the beginning it was evident that any attempt to determine the total nitrogen adsorbed in a large bandage by acid digestion of the entire dressing would be impractical. A technique for sampling was necessary which would yield a sample that not only could be handled by regular laboratory procedures, but would be a representative aliquot of the complete dressing. A large mass of cotton gauze bandage cannot be sampled with any degree of precision. It was essential, therefore, to design a bandage which would be adequate (1) as a dressing in the care and protection of the burned surface, (2) in the collection of all exudate, and finally (3) for aliquoting.

First, we attempted to use large sheets of filter paper. This material readily forms a pulp when mixed in water and yields a uniform suspension. However, it did not prove adequate in adsorbing the exudate from the burned surface. A special dressing was finally devised which appears to meet all of the criteria of adequacy noted. The dressing was designed to simulate as closely as possible the large pressure dressings advocated by Allen and Koch.[3] Closely woven glass cloth* is placed next to the burned surface instead of fine mesh gauze impregnated with petrolatum. A thick layer of Cellucotton† is put on top of the glass cloth to act as the adsorbing agent. The entire dressing is then wrapped with a vinylite plastic bandage.‡ This forms an impervious covering to prevent loss in case the cellucotton should become soaked through. If sufficient cellucotton is applied this does not occur, and ordinary elastic bandages, stockinet, or flannel cut on the bias can be employed. Control analyses of samples of the glass cloth and cellucotton showed them to contain only an insignificant amount of nitrogen.

These dressings were applied shortly after the patients entered the hospital and were changed every five days in conformity with the five-day collection periods which were employed for the nitrogen balance determinations. Occasionally the exudate would soak the dressing sufficiently to require an earlier change. If this occurred, the outer layers were removed and new cellucotton was applied. These dressings did not alter the course of healing in second degree burns. In third degree burns they did not affect the speed with which the slough separated and the granulating surface became ready for grafting. When dressings were removed, the three component parts were placed in separate containers and their nitrogen content determined. The vinylite bandage was washed thoroughly and the wash water added to the cellucotton. The cellucotton was placed in a large metal container to which was

*Fiberglas Cloth (No. ECC-11-108), edges sealed with Vinylite acetone solution to prevent fraying. Obtained from Owens-Corning Fiberglas Corporation, Toledo, Ohio.

†Cellucotton Sheets, prepared for hospital trade. Obtained from Paper Products Mfg. Co., Swarthmore, Pa.

‡Vinylite Plastic Film (No. Vu 1900 Clear .008 thickness), "Highly plasticized Polyvinyl Chloride." Obtained from Carbide and Carbon Chemicals Corp., New York, N. Y.

added sufficient water to make a mush. The cellucotton disintegrated quickly forming a thick suspension which was thoroughly mixed by a motor-driven beater. This entire mixture was weighed and duplicate aliquots, by weight, were removed. Nitrogen determinations were run on these in triplicate. The glass cloth was placed directly in sulfuric acid for digestion of the exudate. All nitrogen determinations were done by the Kjeldahl method.[4]

In order to check the accuracy of this method, several control dressings were moistened with known amounts of plasma and placed on normal skin of unburned patients for five days. The amount of nitrogen recovered from these dressings was approximately equal to the amount of nitrogen which had been added to them as plasma. The presence of bacteria on infected burns produces a different condition from that present when test bandages are used on normal skin. Since some of the bacteria that are present on burned surfaces are capable of forming ammonia, it is possible that nitrogen might be lost in this fashion. In order to determine the importance of this as a source of error, cellucotton was placed in a large beaker and moistened with a known amount of a mixture of plasma and a twenty-four-hour meat extract broth culture of the bacteria obtained from the burns of the patients who were being studied. The mixture was then incubated for five days at 37° C. The amount of nitrogen recovered from these dressings is indicated in Table I.

TABLE I

NITROGEN RECOVERIES FROM PLASMA BACTERIAL MIXTURES AFTER INCUBATION ON CELLUCOTTON AT 37° C. FOR 5 DAYS

NITROGEN ADDED (MG.)	NITROGEN RECOVERED (MG.)	PER CENT RECOVERY
111.6	109.8	98.38
55.1	54.9	99.63
54.6	55.7	102.76
53.8	54.9	102.04

RESULTS

Collections were made from the burns of six patients. A total of nineteen five-day metabolic periods was obtained. The reasons for adopting a five-day balance period have been fully discussed in the monograph by Macy.[4] The patients were cared for on a metabolic ward staffed by specially trained nurses. All of the nitrogen-containing material taken orally or parenterally by these patients was weighed or measured, and duplicate portions or aliquots were analyzed in triplicate for nitrogen. The feces and urine were collected over five-day metabolic periods and handled in a like manner.

The nitrogen loss from the burn varied from 3.0 to 25.47 per cent of the total nitrogen output of these patients. This loss began shortly

after the accident and persisted until epithelization was complete (Table II, Figs. 1, 2, 3, 4, 5, and 6).

The nitrogen in the exudate from the burn was greater, of course, in the larger burns and in these instances contributed significantly to the total nitrogen output. In one patient, C. W. (Fig. 1), the nitrogen lost from the burn alone was approximately equal to that consumed in the diet. During the first ten days following the burn, he lost 390 Gm. of protein from this source. This is equivalent to approximately 7,100 c.c. of plasma.

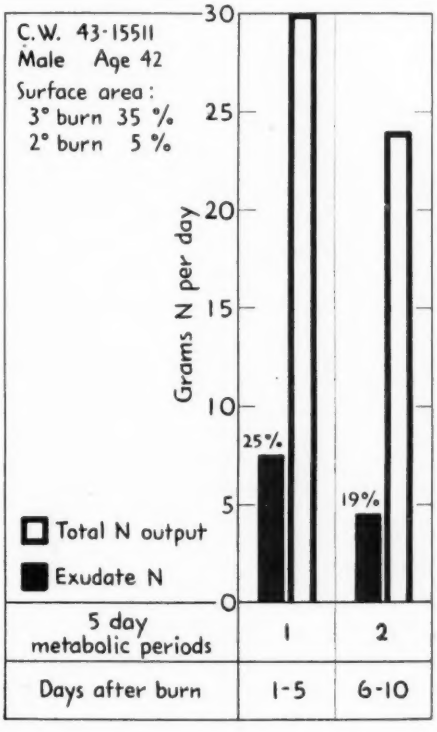

Fig. 1.—C. W. (43-15511), a white man, age 42 years, sustained burns of his face, neck, both arms, shoulders, and entire back when his clothing caught on fire. The burn was mostly third degree and involved about 40 per cent of the body surface. The patient died ten days after the accident. During the first five days following the accident, he lost nearly 8 Gm. of nitrogen a day from the burn. This comprised 25 per cent of his total nitrogen output for this period.

DISCUSSION

Patients who are moderately or severely burned excrete more nitrogen in the urine than can be administered orally as protein without forced feeding. In addition, they lose a significant amount of protein in the exudate from the burned area. Unless a strenuous effort is made to maintain these patients on a very high protein intake, they rapidly become protein deficient. Second degree burns usually heal within ten to twenty days but only a few third degree burns are ready for grafting in twenty-one days. Since most patients can tolerate large protein

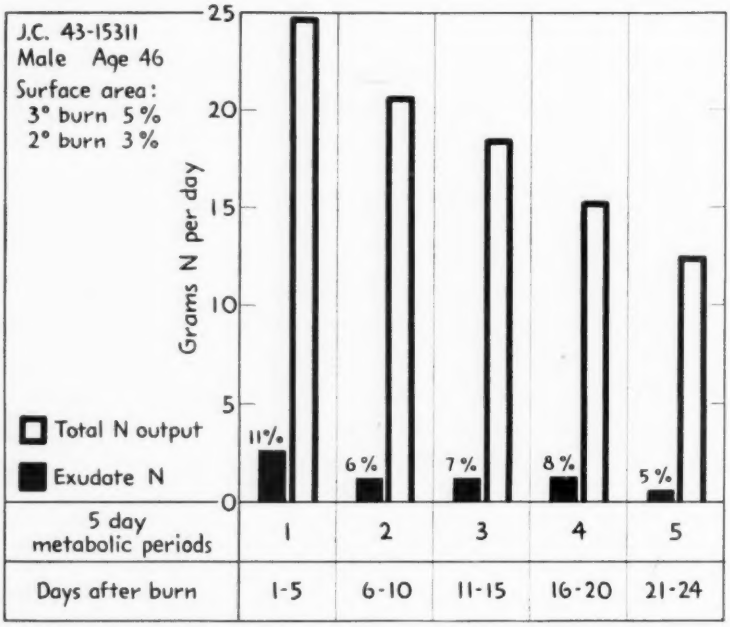

Fig. 2.—J. C. (43-15311), a white man, 46 years of age, suffered burns of both hands and forearms in a gasoline fire. The burn of the left hand and forearm was second degree and healed in about twenty days, while that of the right hand and forearm required grafting. This was done twenty-five days after the accident. The nitrogen loss in the exudate persisted until the burn was grafted, but it decreased about the twentieth day when the second degree areas healed.

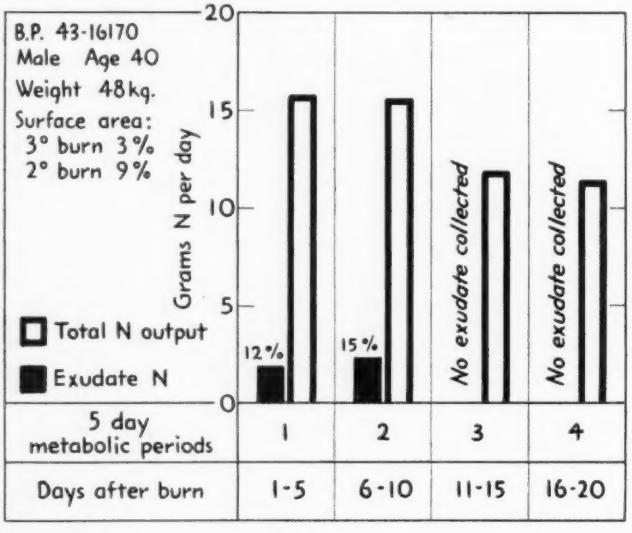

Fig. 3.—B. P. (43-16170), a white man, aged 40 years, sustained second and third degree burns of the face, scalp, neck, shoulders, arms, and forearms when his clothing caught on fire. The burns were separated by areas of normal skin. Approximately 12 per cent of the body surface was involved. During the first five days after the accident the nitrogen in the exudate from the burned area accounted for 12 per cent of the patient's total nitrogen output. From the sixth to the tenth day it comprised 15 per cent of the total nitrogen output. Collections of exudate were not done after the tenth day.

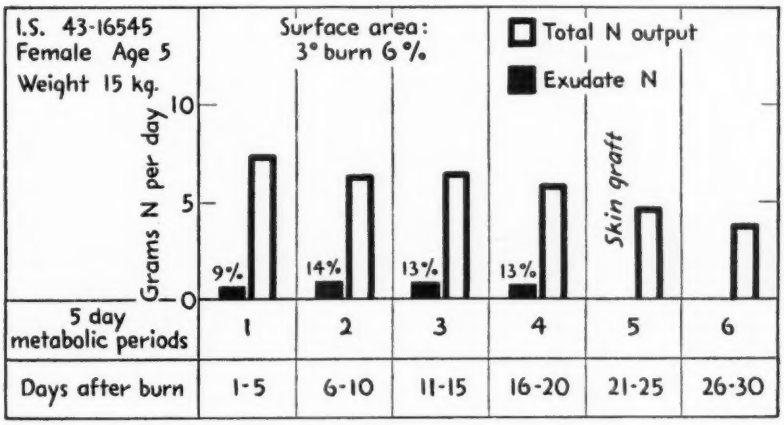

Fig. 4.—I. S. (43-16545), Negro female, aged 5 years, sustained a third degree burn of 6 per cent of the body surface when her clothing caught on fire. Less than 1 Gm. of nitrogen per day was lost in the exudate from the burned area. However, the patient was a small child and although the burn involved 6 per cent of the body surface it was small by actual measurement. The nitrogen loss from the burned area persisted without change till the twenty-first day, when the burn was grafted.

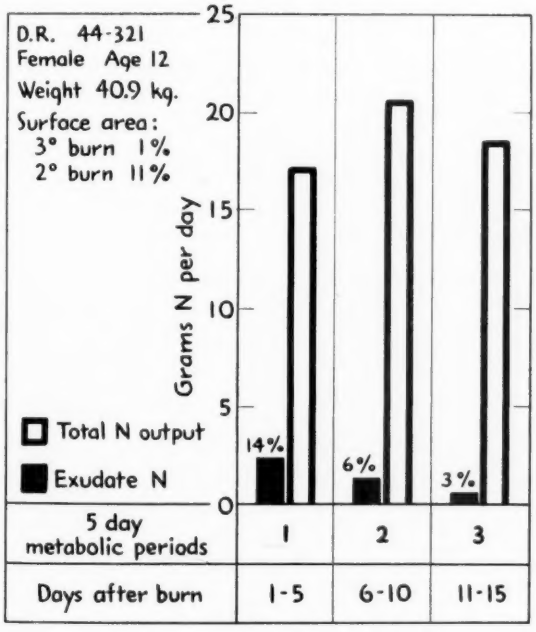

Fig. 5.

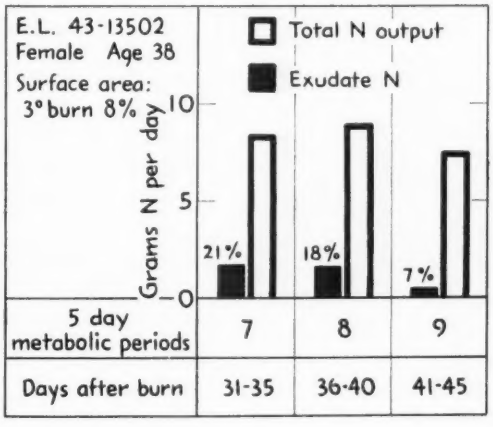

Fig. 6.

Fig. 5.—D. R. (44-321), a Negro girl, 12 years of age, was burned with hot water. The burn involved about 12 per cent of her body surface and was largely second degree. The burn healed rapidly and the amount of nitrogen lost in the exudate from the burned area diminished as healing progressed.

Fig. 6.—E. L. (43-13502), a Negro woman, aged 38 years, was burned by fire on the arm, axilla, and chest. The burn was largely third degree and thirty days after the accident it presented a granulating surface. It is interesting to note that significant quantities of nitrogen were lost from the granulating area at this time. A skin graft was done on the forty-first day after the accident. About 60 per cent of the graft took. This resulted in a decrease in the amount of nitrogen lost from the burned area during the ninth metabolic period.

TABLE II

THE NITROGEN LOSS IN THE EXUDATE FROM THE BURNED AREA IN RELATION TO THE TOTAL NITROGEN OUTPUT

PATIENT	SEX	AGE	SURFACE AREA—SECOND DEGREE BURN (PER CENT)	SURFACE AREA—THIRD DEGREE BURN (PER CENT)	METABOLIC PERIODS OF 5 DAYS EACH															
					I		II		III		IV		V		VI		VII		VIII	
					GM. OF NITROGEN IN EXUDATE PER DAY	PER CENT OF TOTAL NITROGEN OUTPUT	GM. OF NITROGEN IN EXUDATE PER DAY	PER CENT OF TOTAL NITROGEN OUTPUT	GM. OF NITROGEN IN EXUDATE PER DAY	PER CENT OF TOTAL NITROGEN OUTPUT	GM. OF NITROGEN IN EXUDATE PER DAY	PER CENT OF TOTAL NITROGEN OUTPUT	GM. OF NITROGEN IN EXUDATE PER DAY	PER CENT OF TOTAL NITROGEN OUTPUT	GM. OF NITROGEN IN EXUDATE PER DAY	PER CENT OF TOTAL NITROGEN OUTPUT	GM. OF NITROGEN IN EXUDATE PER DAY	PER CENT OF TOTAL NITROGEN OUTPUT	GM. OF NITROGEN IN EXUDATE PER DAY	PER CENT OF TOTAL NITROGEN OUTPUT
B. P.	M	44	9	3	1.97	12.6	2.35	15.0												
I. S.	F	5	0	6	0.72	9.68	0.93	14.7	0.84	13.0	0.76	13.1								
C. W.	M	42	5	35	7.85	25.47	4.64	18.89												
J. C.	M	45	3	5	2.73	11.0	1.31*	6.3	1.42	7.6	1.36	8.8	0.68	5.4						
E. L.	F	38	0	8											1.8	21.3	1.64	18.4	0.58†	7.9
D. R.	F	12	11	1	2.46	14.3	1.36	6.6	0.55	3.0										

*Results for cellucotton only.

†Skin graft performed at beginning of period. Only 60 per cent take.

deficits for a short time, it is in the patients with large third degree burns rather than those with second degree burns that maintenance of a high protein intake is essential. After three weeks of excessive protein catabolism they are still not only excreting abnormally large quantities of nitrogen in the urine but are also losing considerable protein in the exudate from the burned area. Furthermore, instead of being healed they are facing one or more serious surgical procedures. These are the patients who often develop an extreme degree of protein deficiency. The fact that protein in significant quantities continues to be lost in the exudate from third degree burns until they are completely epithelized emphasizes again the importance of early skin grafting.

SUMMARY AND CONCLUSIONS

1. A method has been described for the quantitative collection and determination of the nitrogen lost in the exudate from a burned surface.

2. Complete nitrogen balance studies have been done on six patients with burns and the percentage of their nitrogen output represented by that from the burned surface has been determined. This varied from 3.0 to 25.47 per cent of the total nitrogen output.

3. Nitrogen continues to escape in significant quantities in the burn exudate until epithelization has occurred. This is an additional reason for the early skin grafting of large third degree burns.

David R. Brady of the Department of Pharmacology gave us many valuable suggestions regarding the materials used in the dressings. We wish to express our thanks to him.

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BULLET WOUNDS OF THE LUNGS*

An Experimental Study

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THE observation has been frequently made that through-and-through bullet wounds of the lung may produce little evidence of shock and that they heal quickly and often without evidence of residual damage to the lung. Toward the close of World War I it was observed[1] that tangential nonsucking wounds of the chest were prone to become infected. In recent reports of studies of penetrating wounds of the chest more attention has been given to discussion of the aspiration of blood from the pleural cavity than to the size or location of the wounds in the lung. Elkin and his associates,[2, 3, 4] on the basis of experimental and clinical observations, have advocated conservative or "expectant" treatment of most penetrating wounds of the chest.

Heuer, Pratt, and Mason[1] (in 1920) analyzed 160 patients with penetrating and perforating wounds of the chest cared for in Evacuation Hospital No. I of the American Expeditionary Forces. One hundred and fifteen patients wounded by bullets and shell fragments were not operated upon. The following observations were made regarding the conservative treatment of these injuries: The conditions which predispose to infection are sucking wounds, large retained foreign bodies, and extensive rib fractures. It appears, however, that of eighteen patients who developed infection, seven patients had none of these conditions, and in ten patients who were moribund on admission to the hospital and died within one or two hours after arrival, autopsy revealed in four: "Hemorrhagic consolidation of the lung, not the common type occurring about the wound tract, but involving the lung at some distance from the wound, ... ; in three it involved the lung on the side of the injury; in one, the lung contralateral to the injury." This condition has been recently observed in the Vanderbilt University Hospital.

A 38-year-old white woman was admitted to Vanderbilt University Hospital forty-five minutes after the receipt of a bullet wound of the left upper chest. The wound was inflicted with a .32 caliber automatic pistol, fired at close range. There was evidence of great loss of blood, the continuance of which, after the administration of blood plasma and whole blood, was taken as an indication for exploration of the left chest.

Exploration was through an anterolateral incision which was extended through the left third intercostal space; 1500 c.c. of blood were removed from the left

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pleural cavity. A small wound was found in the surface of the upper lobe, located in the lateral aspect of the lobe about 3 cm. superior to the interlobar fissure. It was 4 cm. in length, about 1 cm. wide, and 1.5 cm. in depth in its mid-portion. Its edges were ragged and there was a continuous, rather copious oozing of blood from its surface. The upper lobe did not collapse and was almost completely filled with dark blood, having the appearance and consistency of liver. A small portion of the apex of the lobe and the anterior division of the lingula segment were the only portions of the lobe which contained air.

Left upper lobectomy was performed. The patient's postoperative course was satisfactory. She was permitted to be out of bed on the eighth postoperative day and was discharged from the hospital two weeks after admission. She resumed her normal activities at home three and one-half weeks after the injury.

Microscopic sections from various areas of the left upper lobe showed the alveoli to be ruptured and filled with blood.

The unusual aspects of this case prompted the experimental studies reported in this communication.

The gross and microscopic appearance of the lesion found in this patient resembled those produced in animals by blast waves. These have recently been described by Clark and Ward[5] in animals exposed to water-borne blast waves. These lesions were shown to be similar to those resulting from blast in air, previously observed and studied by Hooker,[6] Zuckerman,[7] Williams[8] and others. This injury has been shown to be caused by a wave of increased pressure which travels very rapidly and is transmitted through the tissues of the chest wall without inflicting gross injury to the parietes.

Experimental Methods.—Dogs of various weights (5 to 20 kg.) and ages were used. The animals were anesthetized with nembutal, administered intravenously, and were placed on a wooden, angled dog board which rested three inches above a wooden box which was twelve inches deep and filled with sand. They were shot, at ranges varying from one-half inch to thirty-six inches, in the right lower chest. The weapons, cartridges, and ballistics concerned with the cartridges used are shown in Table I.

Immediately after the shot was fired, an incision was made over the right costal cartilages, parallel to the sternum. The cartilages were

TABLE I

TYPE PISTOL OR RIFLE USED	TYPE OF CARTRIDGE	WEIGHT OF BULLET (GR.)	MUZZLE VELOCITY (FT. PER SEC.)	MUZZLE ENERGY (FOOT POUNDS)
.22 Cal. revolver	"Hi-Speed" short	29	1130	82
	.22 "long"	29	1125	81
.32 Cal. automatic pistol (Belgian Browning)	.32 "short"	80	800	114
.45 Colt automatic pistol (U. S. Army model)	Federal arsenal, Govt. Issue, 1934	250	870	421
.257 Mauser (special) rifle	.257 Winchester super X	117	2630	1800
38-55 Winchester rifle	38-55 Winchester	255	1320	985

divided and the right pleural cavity opened widely. In this manner, the lung could be visualized in every experiment within two minutes after the wound was inflicted. Following this procedure the left lung, the chest wall, and in some cases, the abdominal viscera, were inspected for evidences of injury. The lungs were removed, photographs of interesting specimens were obtained at once, and the lungs were placed in 10 per cent formalin solution. Blocks of tissue were obtained for microscopic section after the entire lung had been left in the fixative for several days.

Thirty-three dogs were used in this study. The types of wounds inflicted may be divided into four groups:

1. Through-and-through wounds of the lung
2. Superficial lacerations of the lung

Fig. 1, Group 1 (Expt. No. 29).—Bullet used was .22 caliber. Through-and-through wound of the middle and lower lobes.

3. Wounds of the parietal pleura, but no apparent wound of the lung
4. Wounds of the skin and subcutaneous tissues of the chest wall

Fractures of one or more ribs were usually found in wounds of the types described in groups 1, 2, and 3.

Observations.—Gross estimation of the amount of hemorrhagic consolidation present in the lungs was recorded, and these observations are tabulated in Tables II, III, IV, and V. The observations are recorded as follows:

\+ An area of hemorrhagic consolidation occupying one-fourth of the lobe or less, or diffuse scattered areas of hemorrhage in air-containing lung tissue

++ Firm areas of consolidation involving one-fourth to one-half of the lobe

+++ Firm areas of consolidation involving one-half to three-fourths of the lobe

++++ Lobe completely hemorrhagic, no crepitation, entire lobe deep red in color and as firm to the touch as liver.

Microscopic sections, taken from the areas of hemorrhagic consolidation, invariably showed rupture of the alveolar walls and filling of the air spaces with blood.

Several factors apparently influence the extent and degree of damage to the lung:

The location of the wound and direction of the path of the bullet are of great importance. Through-and-through bullet wounds, even when inflicted with heavy missles having a high "muzzle energy," as the .45 caliber bullet, show far less evidence of widespread damage in the lung than do those of the same missle fired tangentially across the chest and inflicting a small superficial tear of the lung substance. Extensive hemorrhagic consolidation is also caused by a bullet which passes through the deep tissues of the chest wall but which does not inflict a wound upon the lung (Table IV).

The damaging effect of the wave of shock (or blast) created by the impact of the missle with the tissues of the chest wall is transmitted through these tissues to the lung, and may cause widespread disruption of the air-containing lung tissue. This effect is shown most effectively

TABLE II

GROUP 1. THROUGH-AND-THROUGH WOUNDS OF THE LUNG

WEAPON USED	EXPT. NO.	WEIGHT OF DOG (KG.)	DISTANCE: MUZZLE TO CHEST WALL	POSITION OF WOUND	EXTENT OF HEMORRHAGE EACH LOBE				
					RT. LOWER	RT. MIDDLE	RT. UPPER	LT. LOWER	LT. UPPER
.22 Cal. revolver	3		36 in.	Middle lobe		+	++		
.22 Cal. revolver	4	5.0	½ in.	Middle and lower lobes	+	+			
.22 Cal. revolver	5	6.9	½ in.	Lower lobe	++				
.22 Cal. revolver	6*	20.0	½ in.	Middle lobe	++	+			
.22 Cal. revolver	9	4.2	36 in.	Middle and lower lobes	++	+			
.22 Cal. revolver	29	5.8	1 in.	Middle and lower lobes near hilum	++	+			
.32 Cal. automatic pistol	16	11.6	½ in.	Middle and lower lobes near hilum	+	+			
.45 Cal. automatic pistol	35	6.0	½ in.	Right and left lower lobes near hilum	+	+	+	+	

*Surface laceration of the lower lobe.

TABLE III

GROUP 2. SUPERFICIAL (SURFACE) WOUND OF LUNG

WEAPON USED	EXPT. NO.	WEIGHT OF DOG (KG.)	DISTANCE: MUZZLE TO CHEST WALL	POSITION OF WOUND	EXTENT OF HEMORRHAGE EACH LOBE				
					RT. LOWER	RT. MIDDLE	RT. UPPER	LT. LOWER	LT. UPPER
.22 Cal. revolver	1		½ in.	Lower lobe	+++	+			
.22 Cal. revolver	2		½ in.	Lower lobe	+++	+			
.22 Cal. revolver	7	20.0	½ in.	Middle lobe	+	++			
.22 Cal. revolver	30	6.2	1 in.	Lower lobe	+++	+	+		
.45 Cal. automatic pistol	14	12.0	½ in.	Lower lobe	++++	++	++	+	
.45 Cal. automatic pistol	28	11.5	1 in.	Lower lobe	++++	++	++	+	+

TABLE IV

GROUP 3. WOUND OF THE PARIETAL PLEURA, NO PULMONARY WOUND

WEAPON USED	EXPT. NO.	WEIGHT OF DOG (KG.)	DISTANCE: MUZZLE TO CHEST WALL	EXTENT OF HEMORRHAGE EACH LOBE				
				RT. LOWER	RT. MIDDLE	RT. UPPER	LT. LOWER	LT. UPPER
.22 Cal. revolver	8	6.6	36 in.	+++	+			
.32 Cal. automatic pistol	15	15.3	½ in.	++	++	+		
.45 Cal. automatic pistol	12	10.1	½ in.	++++	++			
.45 Cal. automatic pistol	13	6.2	½ in.	+++	++	+		
Winchester 38-55 rifle	18*	8.2	15 in.	+++	++	+		
.257 Mauser (special rifle)	19*	14.3	15 in.	++++	++++	++	++	+

*Parietal pleura intact but overlying ribs adjacent to wound broken.

TABLE V

GROUP 4. WOUND OF SUBCUTANEOUS TISSUE AND SKIN OF CHEST WALL

WEAPON USED	EXPT. NO.	WEIGHT OF DOG (KG.)	DISTANCE: MUZZLE TO CHEST WALL	EXTENT OF HEMORRHAGE EACH LOBE				
				RT. LOWER	RT. MIDDLE	RT. UPPER	LT. LOWER	LT. UPPER
.22 Cal. revolver	11	5.0	36 in.	+	+			
.45 Cal. automatic pistol	20	15.5	2 in.	+++	++			
.45 Cal. automatic pistol	21	15.1	½ in.	+++	+			
.45 Cal. automatic pistol	26*	8.6	2 in.	++	+	+		
.257 Mauser (special rifle)	17 (b)†	9.5	15 in.	+				

*Shot through base of skin flap, previously turned down from chest wall.
†Bullet merely "creased" the skin (did not penetrate).

in the experiments summarized in Table V. In these animals no evidence of injury could be noted in the periosteum, ribs, intercostal muscles, or parietal pleura. The bullets simply "tunneled" through the subcutaneous tissue, creating fairly small wounds of entrance and exit. In one experiment (No. 26) a flap of skin and subcutaneous tissue was dissected from the chest wall and left attached by a

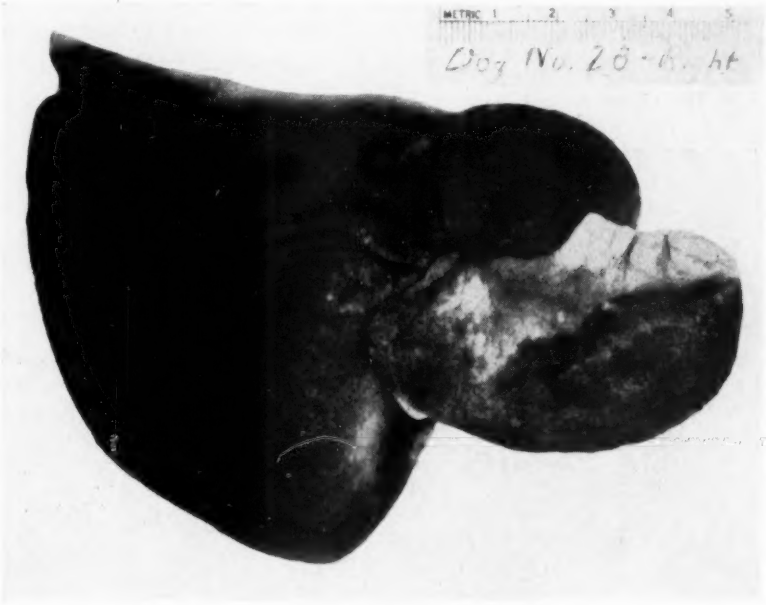

Fig. 2, Group 2 (Expt. No. 28).—Bullet used was .45 caliber. Superficial nick in the costophrenic angle of the lower lobe.

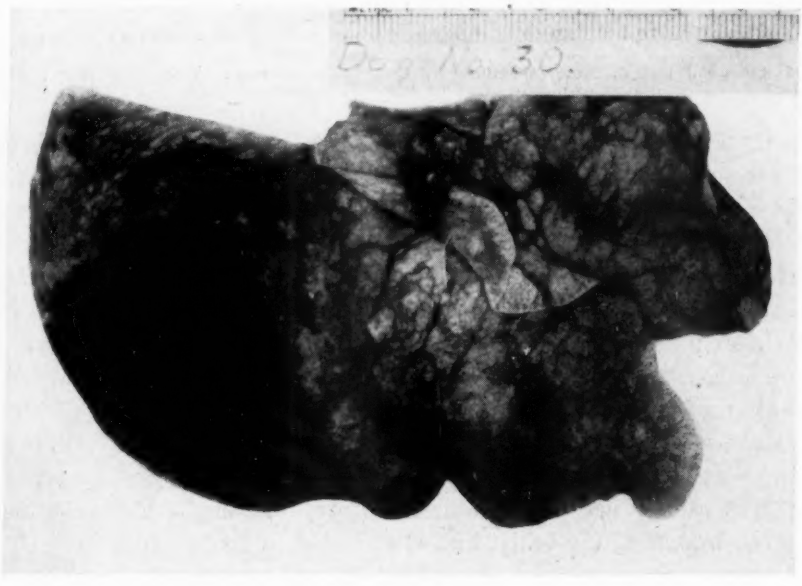

Fig. 3, Group 2 (Expt. No. 30).—Bullet used was .22 caliber. Very small tear through the visceral pleura of the lower lobe.

wide pedicle in the posterior axilla of the right lower chest. A .45 caliber bullet was fired through the base of this flap, about one-half inch from the exposed ribs. The chest was opened immediately and areas of hemorrhage were found in all the lobes of the right lung.

The velocities of the bullets used in these experiments do not vary widely and we have not as yet attempted the use of missles which approach the very high velocity of bomb fragments. It appears, on the basis of one experiment (No. 19), that more widespread damage may be created by the impact of high velocity missles than with slower-moving bodies of the same weights.

Fig. 4, Group 3 (Expt. No. 8).—Bullet used was .22 caliber. Wound of the parietal pleura and intercostal muscles.

On the other hand, the injury was definitely greater with an increase in the weight of the bullet used in various experiments. This is shown by the difference between the lesions observed in animals shot with the .22 caliber revolver and the .45 caliber Colt automatic pistol. The muzzle velocity of the former is greater than the latter, but much more extensive damage resulted from superficial wounds inflicted with the heavy .45 caliber bullet than with the .22. The amount of hemorrhagic consolidation appears to be directly related to the "muzzle energy" of the bullet with tangential wounds of the chest wall and of the lung. This does not appear to be true with through-and-through wounds of the lung, as can be seen in Table II. The muzzle energy of the various cartridges used is shown in Table I. It represents the muzzle velocity times the weight of the bullet and is recorded in foot-pounds.

One experiment was performed in which the muzzle of the .45 caliber Colt pistol was held about 0.5 cm. from the right lower chest wall of a

small animal and fired in such a direction that the bullet passed very close to the animal but did not touch the skin. The bullet penetrated the board on which the animal was lying. The dog's chest was opened immediately and no lesion could be found in the lungs. Blank cartridges, .22 caliber, were also fired, and unless the muzzle of the pistol was pressed against the chest wall no evidence of injury was found. From these observations it was concluded that air-borne blast waves which might have been created by discharge of the bullet at the muzzle are of such low magnitude that they play little or no part in the creation of these lesions. Likewise, the effect of shock transmitted from the board on which the animals lie was shown to be unimportant.

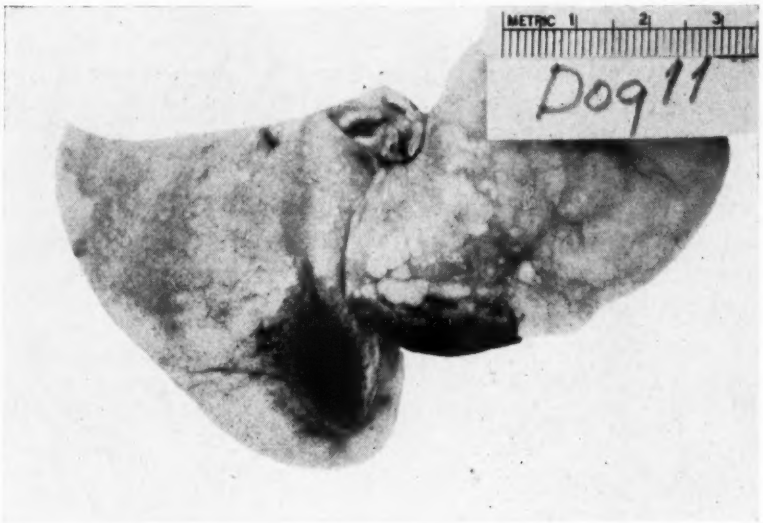

Fig. 5, Group 4 (Expt. No. 11).—Bullet used was .22 caliber. Superficial wound of skin and subcutaneous tissue of chest wall.

In no instances were gross evidences of injury to any of the abdominal viscera observed. Two animals were shot through the abdomen. Multiple perforations of the small bowel were found but no areas of hemorrhage were present in portions of the gastrointestinal tract which were not touched by the bullet. No evidence of injury was found in the lungs of these animals.

The effect of a blow delivered at a much slower velocity was tested by striking, with great force, the right chest wall with a hammer. A rib was broken. A superficial hematoma 1 cm. in diameter lying directly under the visceral pleura and having the appearance of a blister was observed. No other evidence of injury could be found in the lungs.

SUMMARY

1. The immediate effects of bullet wounds of the chest upon the lungs have been observed in dogs.

2. A shock wave which may be comparable to air and water-borne blast waves may be transmitted through the tissues of the chest wall and the lungs. Transmission of this wave of compression, or blast, takes place through the solid, or "fluid," tissues of the chest wall without evidence of damage to those tissues which do not lie within the path of the bullet, and injure the underlying, air-containing tissues of the lung.

3. Rupture of the walls of the alveoli and extravasation of blood into the air spaces were consistently observed in these animals. The extent of the injury and amount of the hemorrhage varied greatly under different conditions.

4. The direction of the course of the bullet is of great importance in determining the extent of damage which is inflicted upon the parenchyma of the lung.

5. The degree of pulmonary injury found in tangential wounds of the chest appears to be directly related to the "muzzle energy," calculated from the weight and muzzle velocity, of the bullet.

6. Rupture of alveolar walls and bleeding into the air spaces of the lung were much more widespread and profuse when the bullet traversed the chest wall tangentially than when it coursed directly through the parenchyma of the lung. This is true whether or not a superficial wound of the lung is created.

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THE SURGICAL TREATMENT OF CHRONIC PULMONARY ABSCESS

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INTRODUCTION

IN THE past few years a well-defined trend toward standardization of therapy in acute and subacute abscess of the lung has been noted. Accurate localization of the abscess in terms of the bronchopulmonary segment involved, accurate orientation in respect to the parietal chest wall, and the use of local anesthesia have increased the safety and effectiveness of early one- or two-stage pneumonotomy for drainage. The results, as demonstrated by others and confirmed by the findings of the present series, warrant considerable optimism.

Unfortunately, however, a large percentage of patients with pulmonary abscess first come to the surgeon in an undeniably chronic stage with one or more of several local complications. These include secondary or multiple abscess formation, chronic organizing pneumonitis with fibrosis and atelectasis, bronchiectasis, and perforation with encapsulated empyema. In the presence of such complications, simple pneumonotomy for drainage may result in immediate improvement, but incomplete recovery. Therapeutic failures are demonstrated by one or more of the following: persistent cough and sputum, recurrent febrile episodes, failure to gain in weight and strength, persistence of secondary anemia and leucocytosis, failure of sinuses and fistulas to heal, and abnormal roentgenographic findings in the chest. Appropriate roentgenographic and bronchoscopic studies will usually demonstrate the nature of complications, and suggest the advisability of secondary pulmonary resection in some form.

With this type of failure in mind from our own case experience and the reports of many others, we have arrived at the conclusion that primary resection without preliminary drainage is the procedure of first choice in chronic abscess when one or more of the following conditions exist:

1. Multiple abscesses or extensive destruction in one or more lobes
2. Secondary bronchiectasis
3. Atelectasis and pneumonitis, unrelieved by bronchoscopic treatment
4. Uncontrolled bleeding
5. Perforation and localized empyema

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With respect to the latter complication, our cases demonstrate that evacuation of the empyema and resection of the involved lobe in a single-stage operation is both technically feasible and reasonably safe.

Case Material.—Included for analysis are all patients with pulmonary abscess who were admitted to the thoracic surgical service of the New Haven Hospital from July, 1938, to the present time. Excluded are cases of abscess complicating bronchiogenic carcinoma or pre-existing bronchiectasis.

Among sixty-six patients, twenty-two were judged to have acute or subacute abscess on the basis of a history covering less than two months from the time of first symptoms to hospital admission. These acute cases do not constitute the subject matter of this study, but for purposes of completeness and contrast are summarized in Table I.

TABLE I

ACUTE PULMONARY ABSCESS

TYPE OF TREATMENT	CURED	MUCH IMPROVED	IMPROVED	POOR	DEAD	UNKNOWN	TOTAL
Conservative (bronchoscopy, etc.)	5	3	0	0	0	0	8
Drainage empyema	3	1	0	0	0	0	4
Pneumonotomy	4	4	0	0	1	0	9
Refused	0	0	0	0	0	1	1
Totals	12	8	0	0	1	1	22

The remaining forty-four patients had chronic abscess and complications, varying in duration from three months to several years. Four patients had already had one or more drainage operations performed elsewhere. Three were critically ill with extensive empyema, and were treated by simple thoracotomy (rib resection). Twenty-two, principally earlier cases, were subjected to one-stage or multiple-stage pneumonotomy. Of these, six subsequently were submitted to pulmonary resection. Together with the four patients in whom drainage was carried out at other hospitals, these made a total of ten secondary resections (seven lobectomies, three pneumonectomies). Fourteen patients were treated by primary resection, all lobectomies. One patient awaited pneumonectomy.

Of the twenty-four patients subjected to primary or secondary resection, fourteen were male and ten female, ranging in age from 6 to 49 years. The average age was 32 years, while the average for all abscess cases was 36. The average duration of the disease was eleven months, excluding two long-term cases. The average patient sought the first medical attention within one month of onset, so that undesirable delay can only be ascribed to ill-advised persistence in conservative treatment by the medical or surgical attendants.

The exciting etiology was clearly apparent in twelve cases, as shown in Table II.

TABLE II

Postoperative, tonsillectomy	7
Postoperative, appendectomy	1
Convulsions, epilepsy	1
Convulsions, eclampsia	1
Trauma to chest	1
Foreign body (surgical gauze)	1

In eleven other cases, a frankly pneumonic onset was recorded; in one case the mode of onset was obscure. Although multilobar involvement due to secondary extension was frequently seen, the principal or primary abscess was located as shown in Table III.

TABLE III

LOCATION OF ABSCESS

LOCATION	NUMBER	LOCATION	NUMBER
R. U. L.	5	L. U. L.	4
R. M. L.	3	L.L. L.	6
R. L. L.	6		
Totals	14		10

Five patients subjected to primary lobectomy had pre-existing perforations with encapsulated interlobar or parietal empyema.

Technique.—A topical anesthesia of pharynx and larynx was carried out with 2 per cent pontocaine and 10 per cent cocaine. If secretions were excessive, the patient was bronchoscoped. General anesthesia was induced with cyclopropane and ether, tracheal intubation performed with woven silk or flexible rubber catheter, and the tracheobronchial tree thoroughly aspirated before the patient was turned into the operative position. In secondary cases, if a draining fistula was present, the wound was packed tightly with dry one-inch gauze in a single strip. This prevents, to some extent, the leakage of gas and reaspiration of secretions and blood.

In the event of a primary resection, the usually accepted approaches (intercostal or rib resection) were made. If previous cautery drainage had been employed, a new incision was planned to avoid the wound area. Where scars or sinuses existed on the posterior or lateral chest wall, an anterior trap-door type of incision was used for the upper and middle lobes. This was a difficult approach for the lower lobe, however, and a long costal incision above or below the drainage area is preferred. After opening the chest, the dissection was directed immediately toward the hilus of lobe or lung. A tentative dissection of the hilus was begun. The feasibility of total resection in preference to mass ligation can be determined only at operation, and bears no constant relationship to the degree of peripheral lung involvement. If individual ligation technique seemed unwise, a Bethune snare was passed to cut off further bronchial spillage, followed by transfixion sutures of chromic No. 1 catgut. If the individual dissection technique was practicable (and it becomes increas-

ingly so with experience in complicated cases), the vessels were freed up. One proximal silk ligature was passed around each vessel on a ligature carrier, followed by a slightly more distal transfixion suture, beyond which the vessel was divided. The bronchus was transfixed by mattress silk sutures, and then divided.

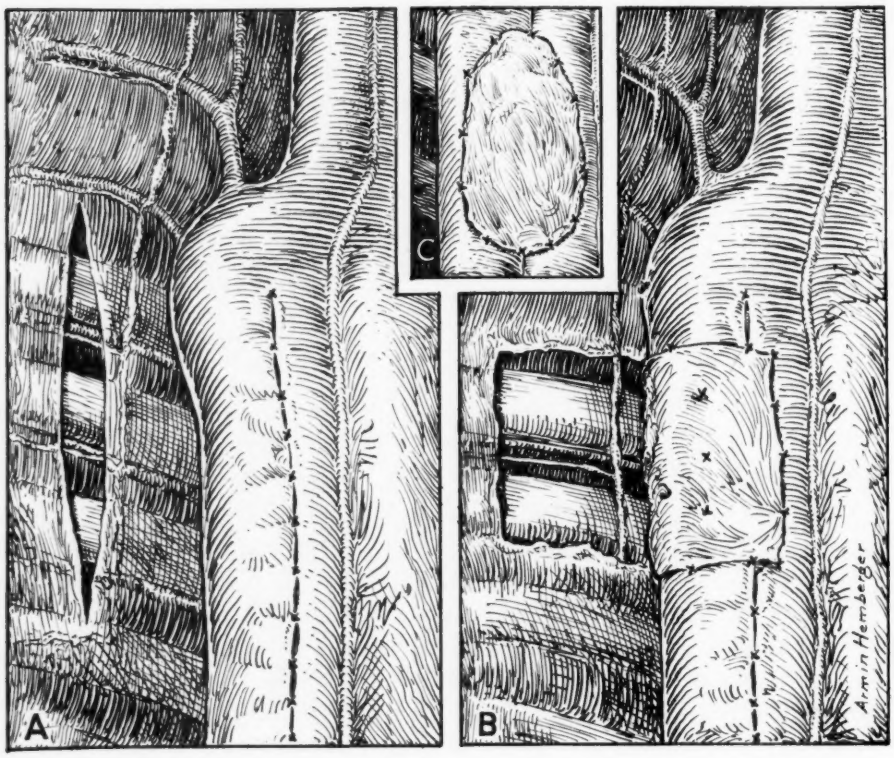

Fig. 1.—Methods of closing the mediastinal pleura following total pneumonectomy. *A*, Counterincision of paravertebral pleura. *B*, Pedicled flap. *C*, Free graft.

Having avoided the dangers of further bronchial spillage, pulmonary arterial bleeding, and embolism, the frequently difficult peripheral dissection was begun. In the region of cautery scars or large sinuses, the collateral circulation through the intercostal arteries may give rise to troublesome and dangerous bleeding. A transfer from the interpleural to extrapleural planes expedited the dissection and decreased blood loss. Sometimes detailed hemostasis proceeded more readily after removal of the lung or lobe.

Closure of the hilus after lobectomy was attempted by leaving a pleuropulmonary flap to turn over the bronchial stump. In the case of total pneumonectomy, complete mediastinal pleural closure is extremely important. Rarely in these cases was sufficient pleura present to effect a linear closure, but this was assisted by a relaxing incision in the paravertebral pleura. If direct closure was not possible, a rectangular pleural flap was turned up to cover the defect, or a free graft

of pleura was used (see Fig. 1). Sulfathiazole powder (4 to 6 Gm.) was scattered over the pleural surfaces.

In the total pneumonectomy cases the pleura was not drained; the lobectomies were all drained. In the secondary cases, the site of previous fistula was useful for the drainage tube, if properly located. Intercostal catheter drainage was used in the primary resections, but was disappointing as compared with short rib resection and a larger tube in the secondary cases. Constant suction was applied to the drainage tube for several days. After total lobectomy, the catheter was removed in a few days if lung re-expansion and relative sterility of drainage fluid permitted.

Immediately at the conclusion of operation, bronchoscopy was employed if secretions had been abundant or tenacious, and during the convalescence as indicated. Blood transfusion was given routinely, and averaged 870 c.c. per operation.

RESULTS

The chronic abscess cases are summarized in Table IV.

TABLE IV

CHRONIC PULMONARY ABSCESS

TYPE OF TREATMENT	CURED	MUCH IMPROVED	IMPROVED	POOR	UNDER TREATMENT	DEAD		TOTALS	MORTALITY PERCENTAGE
						P. O.	LATE		
Drainage empyema	1	0	1	0	0	1	0	3	
Pneumonotomy	5	3	1	6*	1	4	2	22	
Subtotal	6	3	2	6*	1	5	2	25	28.0
Resection, primary	7	5	0	0	1	1	0	14	
Resection, secondary	2	4	0	1	1	0	2	10	
Subtotal	9	9	0	1	2	1	2	24	12.5

*Subsequent secondary resection.

The gross case mortality was ten, or 22.8 per cent.

The drainage operations (thoracotomy and pneumonotomy) contributed seven fatalities, or 28 per cent, and were followed by six poor results, necessitating secondary resection.

The best results were obtained with the fourteen primary lobar resections. In this group there was one death (7.1 per cent), an operative accident. The patient, aged 6 years, had a large post-tonsillectomy abscess in the right lower lobe, of ten months' duration. During operation the abscess evacuated its semisolid content into the trachea and the obstruction was not relieved by bronchoscopy. Among the remaining cases, twelve showed very satisfactory results and in one recent case the patient was under treatment at the time of this writing.

The ten secondary resections included three total pneumonectomies and seven lobectomies. There were no operative (hospital) deaths,

but there were two late fatalities. One occurred in a man 26 years of age, fourteen months after left upper lobectomy for post-tonsillectomy abscess of eighteen months' duration. Death was due to cerebral abscess, verified by craniotomy. The second fatality was that of a male, aged 20 years, four months after left total pneumonectomy for foreign body abscess. The cause of death was streptococcus sepsis following a sore throat, involving heart, pericardium, right lung, and left pleura. The left pleural space had been reported sterile on numerous cultures after operation, and there was no evidence of bronchial fistula. One patient, following right upper total lobectomy, had a disappointingly poor result with residual bronchiectasis in two other lobes. Of two patients still under treatment, when last seen one was doing very well, the other had metastatic cerebromeningeal infection and will probably succumb.

The behavior of the thoracotomy wounds in these patients was interesting. Sixteen of the twenty-four healed per primum; four had minor circumscribed or superficial infection. Two had severe hemolytic streptococcus infections controlled by chemotherapy without disruption, and one had an extensive disruption of the suture line due to mixed infection.

SUMMARY

A series of sixty-six pulmonary abscess cases, observed on the surgical thoracic service at New Haven Hospital in a period of five and one-half years, forms the basis of this report.

The low mortality (4.5 per cent) and excellent end results of therapy in acute abscess are contrasted with the high mortality (22.8 per cent) and poorer end results in chronic abscess.

In the chronic abscess group, primary lung resection was associated with lower mortality (7.1 per cent) and better results than other types of treatment.

Secondary resection after previous drainage operations was useful for the salvage of otherwise unsuccessful cases. This operation was followed by no immediate mortality but a higher incidence of late complications and deaths which increased the eventual mortality of all resections to 12.5 per cent.

SURGICAL TREATMENT OF BRONCHIECTASIS

Factors Influencing Postoperative Morbidity and Mortality

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THE results of surgical treatment of bronchiectasis have improved greatly during the past decade. A considerable number of reports on the mortality following lobectomy and pneumonectomy for bronchiectasis have appeared in the literature, but in only a few instances have the postoperative complications been analyzed in detail. During 1940 to 1943, I have performed or directed sixty-four pulmonary resections for bronchiectasis. Included in the series are cases of residual bronchiectasis following drainage of a pulmonary abscess, and also cases of cystic disease of the lung. The series consists of fifty-five lobectomies and nine pneumonectomies, with one operative death, or a mortality rate of 1.6 per cent. The postoperative complications in the fifty-seven cases of this series in which I personally directed the postoperative care have been analyzed. The factors which influence postoperative morbidity and mortality are discussed on the basis of this series and also from observations made at clinics with which I am associated.

Selection of Patients.—The patients ranged in age from 4 years to 57 years. The bronchiectasis was bilateral in twelve cases, and involved more than one lobe in almost one-half of the cases. Marked pulmonary fibrosis and emphysema were present in only a few instances, but moderate degrees of fibrosis and emphysema were present rather frequently.

Operative Procedure.—The operations have been performed under intratracheal oxygen-ether or cyclopropane anesthesia. A one-stage operation has been employed. Although many patients in this series were operated upon by the tourniquet technique, dissection and individual ligation of the hilar structures are now considered desirable if the patient's condition or inflammatory infiltration of the hilar region does not increase the risk of this operative technique. In some cases partial lobectomy of one or two lobes has been performed.

Complications During Operation.—In my experience the maintenance of a clear airway by the anesthetist has been the most important single factor in the patient's condition during operation. If the patient's pulmonary ventilation is entirely satisfactory, the surgeon can perform the operative procedure in a careful manner. If the airway cannot be rendered satisfactory, the operation is postponed or interrupted. In this series of cases no serious hemorrhage or other surgical accidents occurred during the operation. In one instance in which a lobectomy for

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dry bronchiectasis with frequent hemoptysis was begun, serious hemorrhage from the pulmonary artery resulted during an attempt to free this vessel. The hemorrhage was controlled by ligation of the branch of the pulmonary artery to the involved lobe, but the lobectomy was not completed. The hemoptyses, which had been a frequent occurrence prior to operation, were not present during the year after operation.

Relatively little difficulty has been encountered in the maintenance of good peripheral circulation throughout the operative procedure. All efforts are directed toward minimizing the blood loss. Intravenous fluids are given throughout the operation; blood transfusions are begun early. One or two transfusions are given in most instances during operation. In many instances there has been relatively little change in the patient's condition throughout the entire operative procedure, and shock has been rarely encountered. The operations have usually varied from three to four hours in length.

Postoperative Complications Following Lobectomy.—Collapse of the remaining pulmonary tissue on the side operated upon is one of the most frequent and serious complications following lobectomy for bronchiectasis. Among forty-eight lobectomies in our series in which frequent roentgenographic studies were made in the early postoperative period, there were five cases of postoperative collapse of the remainder of the lung on the side of operation. Postlobectomy collapse occurred four times in a series of forty lobectomies of the lower lobe, and once in eight cases of the upper lobe. In three of the four instances of collapse of the remaining upper lobe, the left lower lobe had been resected. In the single instance of collapse of the upper lobe following removal of the right lower lobe, the patient had situs inversus, and therefore the right lung anatomically resembled the left lung of a normal individual. As there has been much discussion in the past concerning the role of pleural adhesions in the avoidance of postoperative pulmonary collapse, our data on this point were analyzed. In twenty-two of the forty patients subjected to lower lobe lobectomy, there were few, if any, adhesions over the upper lobe. In the remaining eighteen cases, a considerable number of adhesions were present over the remaining lobe, and in six instances the unresected lobe was completely adherent. In all five cases in which postoperative collapse of the remaining lobe followed lobectomy, there were few, if any, adhesions over the unresected portion of the lung.

In three of the four instances in which collapse of the left upper lobe followed a lobectomy of the lower lobe, bronchiectasis was probably present in the lingular portion of the upper lobe which was not removed. Certainly in one of the three cases the lingula was definitely involved, and in this instance the postoperative pulmonary collapse was most marked, and of longest duration. Three of the four patients with postoperative collapse of the upper lobe had bilateral bronchiectasis, and

large amounts of sputum were present preoperatively in three of the four. In none of the cases was the collapse of the upper lobe permanent. In one instance the lobe reinflated immediately following bronchoscopy; in a second case the upper lobe remained well aerated after the eleventh postoperative day following several bronchoscopies; and in a third patient the lung collapsed intermittently during the first week after operation, but remained well aerated thereafter. In the fourth case of postoperative collapse of an upper lobe following lobectomy of the lower lobe, an empyema without bronchopleural fistula developed and there was a six-week interval from the time of collapse of the upper lobe until the empyema cavity was obliterated by re-expansion of the upper lobe. In the single instance of collapse of the lower and middle lobe following a lobectomy of the upper lobe, reaeration occurred in two weeks following two bronchoscopies. The patient had relatively little sputum and a nonadherent lower and middle lobe.

In two cases there was considerable accumulation of fluid within the pleural space on the side operated upon in spite of the presence of a drainage tube. Thoracentesis was performed with satisfactory results. Readjustment of the drainage tube was frequently necessary in order to maintain adequate pleural drainage. No serious infection of the chest wall wound occurred in this series, but localized infection of the wound occurred in several instances.

A secondary thoracotomy for empyema was performed in five of forty cases of lower lobe lobectomy. In one of the patients a chest wall sinus at the site of a previous drainage of a pulmonary abscess was present at the time of lobectomy. Of the cases with no preoperative sinus, in one instance an empyema followed pulmonary collapse, and in a second case an apical empyema developed following a spontaneous tension pneumothorax in the apical portion of the pleural space occurring on the twenty-second postoperative day in a patient with moderate pulmonary fibrosis and emphysema. In a third case a foul empyema required a thoracotomy, and complete healing did not occur until two months postoperatively; and in the fourth case a small pleural abscess was present around the bronchial stump following a hilar dissection type of lobectomy. In no instance was any thoracoplastic procedure necessary following a lobectomy of the lower lobe.

In two cases a thoracotomy was performed for an empyema localized near the bronchial stump following a lobectomy of the upper lobe. In one additional case an upper stage thoracoplasty was necessary to obliterate a residual pleural space following upper lobe lobectomy.

In all patients with lobectomy for bronchiectasis drainage was instituted. In some cases the drain was removed as early as forty-eight hours following operation, but in the majority of instances, particularly if a tourniquet type of lobectomy was performed, the drain was left in place for about two weeks. Although some of these patients had a

temporary bronchial fistula and there was drainage of some purulent material for a short period, no secondary operative procedure was necessary except as already indicated, and the late result was not unfavorably influenced.

The one death in the series resulted from extensive bronchial secretion, chiefly in the contralateral lung. The patient's condition during and at the conclusion of the operation was excellent, and there was no evident aspiration of infected material into the opposite side. The patient died five days after lobectomy. Autopsy revealed widespread bronchiolitis, chiefly in the contralateral lung. Whether the pulmonary pathology was originally on the basis of infection could not be definitely ascertained. If bronchoscopy had been employed shortly after operation, the outcome might perhaps have been altered.

Complications Following Pneumonectomy.—The postoperative condition of the nine patients following pneumonectomy was satisfactory. In one case there was bronchiectasis in the contralateral lung and some difficulty was encountered in expectoration of the bronchial secretion during the first few days after pneumonectomy. One patient showed radiographic evidence but few clinical signs of infiltration in the contralateral lung, which cleared in two weeks.

In four cases no drainage was instituted at the time of pneumonectomy for bronchiectasis. Two of these patients never developed any pleural infection, whereas a third patient required a thoracotomy in the early postoperative period, and the fourth patient had a late empyema three months after pneumonectomy. In five patients drainage was instituted at the time of pneumonectomy. Three of these patients required no further operative procedure following removal of the tube. Two of these three were children. Two patients in whom drainage was instituted at the time of operation required a secondary thoracotomy for more adequate drainage, and later a thoracoplasty. The patients who required a secondary drainage in the early postoperative period had a bronchial fistula. The patient in whom an empyema developed three months after pneumonectomy has never had evidence of bronchial fistula, and the empyema space was obliterated by a two-stage thoracoplasty.

Postoperative Results.—In fifty-nine cases the period of follow-up was of sufficient duration that a tentative evaluation of the postoperative result was possible. In forty-two cases the result may be classified as excellent or good. Ten patients had some cough and sputum from residual bronchiectasis. In all except one of these patients there was a marked improvement over the preoperative status. Four patients had pulmonary hemorrhages after lobectomy, but were otherwise in good condition. One patient with known tuberculosis prior to operation had an occasional positive sputum after lobectomy. In another patient in whom tuberculosis was first diagnosed following lobectomy there

was clearing of a tuberculous spread in the contralateral lung. A child who underwent a pneumonectomy had a residual empyema cavity because thoracoplasty was postponed. Two patients died in the follow-up period; in one instance death was due to pneumonia in the contralateral lung several months following lobectomy for bilateral bronchiectasis. In the second case a carcinoma of the main bronchus was diagnosed one year following lobectomy on the same side.

DISCUSSION

The factors influencing operative morbidity and mortality following pulmonary resection for bronchiectasis may be considered in three categories: first, factors relating to the preoperative condition of the patient; second, events during the operative procedure, and third, the management of the patient postoperatively.

Preoperative Factors Affecting Incidence of Postoperative Complications.—The severity of the bronchiectasis, but more particularly the distribution of the involved bronchi, will naturally play a significant role in postoperative complications. If the bronchiectasis is entirely limited to one lobe, lobectomy results in complete extirpation of the infected bronchi. Frequently, however, some bronchiectatic changes are also present in other portions of the same or in the opposite lung. In the former instance the involved bronchi in the second lobe can be removed with the lobe which is the seat of the major disease. For example, it is frequently indicated to remove the lingular portion of the left upper lobe together with the entire left lower lobe. Similarly, on the right side the middle lobe may be removed together with the right lower lobe. If it is feasible to remove all the diseased tissue, the incidence of serious postoperative pulmonary complications is much less than if any bronchiectatic pulmonary tissues remain, especially on the side of the operative intervention. It seems to be of greater significance to have the remaining pulmonary tissue on the side operated upon normal than to have an entirely normal contralateral lung. Although some of our patients had bilateral bronchiectasis, we have had little difficulty with postoperative complications in the contralateral lung. On the other hand, even a relatively slight degree of bronchiectatic involvement in the remaining pulmonary tissue on the side of operation has frequently been a factor in postoperative morbidity.

The degree of pulmonary fibrosis and emphysema should be considered in evaluating the patient's status. Due to the constant presence of infection within the tracheobronchial tree as a result of bronchiectasis of one lobe, progressive damage may occur throughout both lungs. When an acute pneumonic process occurs in the course of chronic bronchiectasis, the pneumonitis is frequently present in portions of the same or opposite lung which are free of bronchial dilatations.

It has been my impression that the presence of pulmonary fibrosis and emphysema increases the hazard of any type of operative intervention. The degree of this type of pathologic change should be given consideration in deciding on the advisability of pulmonary resection for bronchiectasis, particularly in the older age group. A lung which is the seat of pulmonary fibrosis and emphysema has a poor resistance to infection. The loss of elasticity of the pulmonary parenchyma seriously impairs the ventilatory function. Moreover, correlation between ventilation and circulation is readily disturbed and may easily result in impaired oxygenation of the blood, with resultant anoxia. The insidious progression of fibrosis and emphysema throughout the lungs is a strong argument in favor of early, adequate surgical therapy in those cases of bronchiectasis in which radical treatment is feasible. In the series of cases of bronchiectasis treated by lobectomy which have been reported, the operative mortality has been lowest in the younger age group.

The main objects of the preoperative preparation of the patient are: (1) to obtain a maximum subsidence of the inflammatory process in the bronchial walls and adjacent pulmonary parenchyma, (2) diminution in the amount of bronchial secretions, (3) diminution in the virulence of the bacterial flora of the tracheobronchial tree, and (4) improvement of the patient's general condition.

Since bronchiectasis is a chronic disease with exacerbations and remissions depending on the degree of activity of the bacterial infection, the operation should be performed during a remission. Only rarely is operation indicated in the face of local and systemic signs of acute infection. Continued hemorrhage may occasionally urgently indicate a lobectomy, but in many such cases infection is not a marked feature. It may be advisable to allow weeks or months to elapse before performing a lobectomy. This is, naturally, in contrast to the indications in some other types of pulmonary suppuration, such as multiple pulmonary abscess. Some surgeons have preferred to perform elective lobectomies in bronchiectasis only in the season of the year in which the incidence of respiratory infections among the general population was relatively low.

Postural drainage and bronchoscopic aspiration play an important role in preparing a patient for pulmonary resection. By these measures a marked reduction in the amount of bronchial secretion may occur. As a result of lessening of the stagnation of purulent material in the dilated bronchi, a fetid type of bronchiectasis may temporarily become nonfetid.

Sulfonamide therapy is of value in the preoperative preparation, particularly if there is clinical evidence of infection present. Sulfonamides administered orally result in a satisfactory concentration of the drug in the bronchial secretions.

In the absence of serious, prolonged, acute infection, the patient with chronic bronchiectasis is usually in a relatively good nutritional status. Not infrequently the patient's general appearance belies the serious nature of the pulmonary lesion. If, due to a recent flare-up of the infection, a deficiency state exists, this should be corrected preoperatively by adequate therapy. Anemia, vitamin deficiencies, and hypoproteinemia should be corrected by the usual measures.

Events During Operative Procedure Which Influence Postoperative Morbidity and Mortality.—The early literature on pulmonary resection contains many reports of death during or immediately following operation as a result of asphyxia, hemorrhage, and cardiac failure. It is my firm conviction that relatively few of the deaths listed as due to cardiac failure were primarily caused by a damaged myocardium. Certainly in most instances the cardiac collapse was secondary to serious disturbances in intrathoracic physiology and usually associated with severe anoxia. If adequate attention is directed to the avoidance of cardiac damage by anoxemia or direct irritation of the heart by operative manipulation, relatively few patients in whom surgery is indicated for bronchiectasis will die as a result of cardiac failure.

The prime considerations in lessening the hazards at the time of operation are: (1) maintenance of an unobstructed airway, (2) adequate pulmonary ventilation to insure adequate oxygenation of blood, (3) the avoidance of unnecessary reflex stimulation by surgeon and anesthetist, (4) careful operative technique with emphasis placed on the avoidance of trauma and blood loss, rather than efforts directed to reducing the length of the operation, and (5) reduction of the physiologic disturbances necessitated by the operative intervention to a minimum.

In a disease in which large quantities of infected secretion are present in the air passages even prior to the induction of anesthesia, the problem of maintenance of an adequate airway may be particularly great. If bleeding from the bronchi should be present at the time of operation, the risks are greatly increased because of the possibility of obstruction from a blood clot. The great responsibility of the anesthetist in the maintenance of a clear airway during thoracic operations has been discussed at considerable length elsewhere.[1]

The airway cannot be considered ideal if there is any degree of anoxemia present, or any obstruction to ventilatory motion of either lung. Cyanosis is usually only evident when a considerable degree of anoxemia is present and should always be considered a potentially dangerous sign. In my experience a thoroughly satisfactory airway in cases of bronchiectasis can be assured only if an intratracheal tube is utilized. The theoretical objections which may be raised against the use of an intratracheal tube seem to be far outweighed by the practical advantage it affords. Because of obstruction in the airway there may be interference with pulmonary ventilation. By attempting to inspire against a re-

sistance, an abnormally great negative pressure is developed in the bronchial system. Drinker and Warren[2] have demonstrated that a markedly negative intrabronchial pressure has a suctionlike effect on the fluid in the capillaries and interstitial tissues, and results in fluid accumulation in the alveoli. Such an occurrence may be the forerunner of atelectasis or pulmonary edema. The lung on the side operated upon should be inflated at regular intervals by the anesthetist to lessen the hazard of postoperative edema of the pulmonary tissues.

Reflexes may at times be the source of serious difficulty for both anesthetist and surgeon. Most of the reflexes with which we are concerned in thoracic surgery are mediated through the vagus. The anesthetist may initiate reflexes by manipulation in the pharynx, larynx, or tracheobronchial tree. The surgeon may cause vagal reflexes by traction on mediastinal structures or by the application of a tourniquet or clamp on the bronchus. The injection of procaine around the pulmonary hilum prior to resection has been recommended in order to block the vagal impulses from the operative site. In some instances this seems to be of definite value. In view of the meager information that is at present available concerning the effect of nerve impulses on the control of the interstitial fluid balance in the lung, it is not yet certain whether blocking of the vagus has any undesirable side effects. If the surgeon should cause marked brachycardia or apnea by vagal stimulation, it is of the utmost importance that the operative manipulation be temporarily interrupted in order to permit the patient to regain fully his equilibrium.

The development of the technique of hilar dissection for a lobectomy has re-emphasized the importance of meticulous care in operative technique. This type of operation cannot be carried out safely if speed is considered to be of great importance. I feel that it has been conclusively demonstrated that if the patient's pulmonary ventilation is entirely satisfactory and the blood loss during operation is moderate, prolonged intrapleural operative procedures can be performed with relatively little fear of shock.

Factors in Postoperative Management Which Influence Morbidity.—The chief considerations in postoperative management are: (1) the avoidance of retention of bronchial secretions, (2) the early expansion of the remaining pulmonary tissue on the side of operation, and (3) the avoidance of anoxia.

It is essential that the tracheobronchial tree be cleared of secretion before the patient leaves the operating room. In many clinics postoperative bronchoscopy is a routine procedure. Certainly if there is any question concerning the thoroughness with which the secretions have been removed by catheter suction of the trachea, a bronchoscopy should be performed. As soon as the patient regains consciousness he should be urged to cough, in order to clear the air passages. Catheter suc-

tion of the pharynx and trachea must be utilized at the slightest indication of retained moisture in the tracheobronchial tree. If the secretions are thoroughly removed early, the tendency for further secretions to develop will be less pronounced. Constant nursing care directed toward elimination of bronchial secretion is most essential. If these factors are not thoroughly realized, the morbidity and mortality for pulmonary dissection for bronchiectasis, especially if bilateral, will be much greater than necessary. If at any time the secretions cannot be effectively evacuated by coughing, on the part of the patient, some type of suction must be employed. The method of intratracheal suction advocated by Haight and Ransom[3] has proved most valuable. If this procedure does not adequately remove the secretions, bronchoscopy should be performed without delay. It is my impression that bronchoscopy is often delayed too long. An expertly performed bronchoscopy is not a particular ordeal for most patients, and they often feel more comfortable following the procedure because of easier respiration. Retained bronchial secretions are the most important single factor in producing postoperative pulmonary collapse. If even a small degree of bronchiectasis is present in the remaining lobe on the side of operation, the possibility of collapse is increased due to the difficulty in expelling the secretions.

Early expansion of the remaining lobe greatly reduces postoperative morbidity. I am in thorough accord with those who feel that, at least with modern surgical technique, the pleural complications following lobectomy are chiefly secondary to intrapulmonary complications. If the remaining pulmonary tissue can adequately re-expand, serious pleural infections are now uncommon. If the lobe fails to expand, an extensive empyema may be feared in addition to the consequences of the intrapulmonary process itself. In the series of 154 cases from the Brompton Hospital analyzed by Gowar,[4] 33 per cent of the patients had postoperative collapse of the lung following lobectomy. More than one-third of all the deaths were due to secondary suppuration in the unexpanded lobe. In the series of cases he analyzed, there was a mortality rate of 5.8 per cent from this one cause alone. Although Gowar did not place great emphasis on retention of bronchial secretion as a cause of the complications, it is my own impression that constant attention directed toward the avoidance of retained bronchial secretions will greatly lessen this hazard. In my series there was a 10 per cent incidence of collapse of the upper lobe following lower lobe lobectomy, and in each instance the lobe re-expanded without evident permanent damage.

I agree with Chesterman[5] that postoperative collapse of the remaining lobe is the most important single factor in postoperative morbidity. The role which the presence or absence of pleural adhesions over the remaining lobe plays in the development of postoperative col-

lapse is the subject of considerable debate. Gowar[4] analyzed the influence of adherence of the remaining lobe in relation to postoperative pulmonary collapse. In a series of 154 lobectomies for bronchiectasis performed at the Brompton Hospital, there were fifty-one cases of postoperative collapse. In the group of cases in which no adhesions were present, the incidence of collapse was 48.6 per cent; in cases in which the remaining lobe was partly adherent the incidence of collapse was 24.2 per cent, whereas in cases in which the remaining lobe was adherent to the chest wall, only 17.7 per cent had postoperative collapse of the upper lobe. An analysis of my cases also indicates the greater likelihood of postoperative pulmonary collapse if the remaining lobe is free. The presence or absence of pleural adhesions, however, is not the primary factor in the production of pulmonary collapse. It is rather the obstruction of the bronchus of the lobe by retained secretion, or other factors which prevents air from entering the lobe and thus expanding and filling the hemithorax. It is my feeling, therefore, that all efforts should be directed to the removal of bronchial secretions rather than the production of pleural adhesions prior to lobectomy.

Gowar[4] found that massive collapse occurred nearly two and one-half time more frequently in lobectomy of the left side than after operation on the right side. He thought that this occurrence might be explained by the anatomic arrangement of the left upper lobe bronchus, which would favor the retention of secretion during an operation performed in the head-down position. Also, edema of the orifice of the upper lobe bronchus might result from operative manipulation in the hilar area. Another factor which must be taken into consideration is the possibility of injury to the blood vessels of the upper lobe during a lower lobe lobectomy, especially on the left side. Obstruction of a pulmonary artery is followed by shrinkage and collapse of the corresponding portion of the lung with the late development of fibrosis. In my series all of the cases of pulmonary collapse occurred on the left side, except in a case of situs inversus. The predominance of pulmonary collapse of the left side cannot be entirely accounted for by the greater frequency of bronchiectasis on the left side, because in almost one-third of my cases the right lower lobe was operated upon. The great frequency of bronchiectasis in the lingular portion of the left upper lobe may well be a factor of importance.

The remaining pulmonary tissue on the side operated upon will not re-expand satisfactorily if there is an accumulation of fluid or air within the pleural space. Therefore, adequate closed drainage in the early postoperative period is most helpful. A tube of sufficient size must be properly placed, especially in relation to the diaphragm, in order to assure the evacuation of air and fluid from the pleural cavity during the first day or two after operation. If loculation of pleural fluid occurs, thoracentesis is indicated.

In the early period of pulmonary resection it was considered a great advantage to have the upper lobe adherent to the chest wall if the lower lobe was to be resected, and therefore a two-stage operation was advocated. Intrapleural operations at that time were attended by a high incidence of empyema, and the pleural infection frequently involved the entire hemithorax unless the upper lobe was broadly adherent. Experience has shown, however, that the most important single factor in reducing the incidence of postoperative empyema after lobectomy is the early complete re-expansion of the remaining lobe, so that the pleural space on the side operated upon is obliterated shortly after operation. The expansion of the remaining lobe over the stump of the resected lobe greatly lessens the incidence of bronchial fistula and empyema. If a hilar dissection type of lobectomy has been performed and the remaining lobe expands well, an empyema of clinical significance is uncommon. Therefore, at the present time it is not considered necessary by many surgeons to have adhesions over the remaining lobe prior to lobectomy. In fact, adhesions over the remaining lobe may interfere with rapid expansion of that lobe and early obliteration of the pleural space. On the other hand, if the remaining lobe remains collapsed or re-expands poorly, the incidence of empyema will be high.

Following pulmonary resection there is often a mild degree of anoxemia which may last for several days even in the absence of serious postoperative complications. Obviously, any obstruction to the airway or pneumonic process in the remaining pulmonary tissues can cause serious anoxemia. Maier and Cournand[6] have shown that there may be a more prolonged and severe degree of anoxemia after an uncomplicated lobectomy than following pneumonectomy. This is explained by the fact that the remaining lobe on the side operated upon ventilates poorly in the early postoperative period, while the pulmonary circulation through that lobe is not correspondingly reduced. This imbalance between ventilation and circulation results in inadequate oxygenation of the blood leaving the remaining lobe on the side operated upon. Oxygen therapy is therefore indicated in the postoperative period, particularly if there is any question of impairment of the coronary blood flow.

SUMMARY

A series of sixty-four consecutive cases of bronchiectasis in which pulmonary resection was performed is presented. In fifty-five cases a lobectomy was done, and in nine cases a pneumonectomy was performed. There was one operative death in the entire series, giving a mortality of 1.6 per cent.

The postoperative complications are analyzed.

Factors which influence the morbidity and mortality of pulmonary resections are discussed.

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THE SURGICAL TREATMENT OF CONGENITAL ATRESIA OF THE ESOPHAGUS

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CONGENITAL anomalies of the esophagus occur in considerable variety but as yet no classification has been commonly agreed upon. Many of these anomalies are exceedingly rare and are described only in grossly malformed monsters, and most of them are, or have been considered, incompatible with life. There is, however, a group which occurs relatively frequently and as the only anomaly offering a serious threat to survival often enough to challenge surgical intervention. For the purposes of a discussion of treatment, therefore, the all-inclusive classifications such as those of Phelps[16] or Strong and Cummings[25] seem less useful than the simpler classification of Vogt,[15] who lists three types: (1) complete absence, (2) atresia without tracheal fistulas, and (3) atresia with fistulas between the trachea and the esophagus. The latter is further subdivided into (a) those with a fistula between upper segment and trachea, (b) those with a fistula between lower segment and trachea, and (c) those with fistulas between both segments and trachea. The first type cannot be treated, but the second and especially the third, which includes the great majority of reported cases, are now being treated surgically with increasing success.

All of these anomalies are said to arise as developmental defects, rather than as the result of mechanical effects upon the growing fetus. Differentiation of the trachea from the esophagus is not a simple process of budding, but rather a complex combination of differing rates of growth which normally results in separation of the structure not only by downward growth of the tracheal bud, but also by an upward infolding of the walls of the primitive gut which unite to form an intervening septum. If the latter is incomplete or faulty, an anomaly results. This concept has been emphasized by Zeit[3] and Rosenthal[18] and more recently expanded by Gruenwald.[37] It appears to explain the most common type of anomaly (3b) but is not altogether satisfactory in accounting for the less usual ones. But whatever the etiology, the anomalies follow a consistent pattern and so presumably have a common cause.

Characteristically babies born with this anomaly present little evidence of it at birth, except that they may have somewhat more pharyn-

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geal mucus than usual and not infrequently require resuscitative procedures to establish breathing. During the first twenty-four hours cyanotic spells are likely to be frequent, associated with the appearance of considerable frothy mucus in the mouth and nose. If the baby is vigorous, however, he may at first take care of this quite well and not become sufficiently cyanotic to be alarming. Real trouble is often not suspected until attempts at feeding result in immediate regurgitation of the fluid accompanied by alarming respiratory distress. In any infant showing these symptoms the anomaly should be suspected. If attempts to feed the baby are persisted in, aspiration pneumonitis rapidly develops and at the same time the baby becomes dehydrated. If the fistula between the trachea and lower segment is a large one, air will be passed downward through the lower segment into the stomach and will soon cause distention of the small intestine. The baby may pass meconium, especially during the first day or two, but this will be small in amount.

Diagnosis can be verified simply and safely by passing a small catheter into the esophagus. This will pass readily into the stomach in any normal infant. If it meets obstruction at the level of the thoracic inlet, and this may be verified by fluoroscopy, the diagnosis can be made definitely. Attempts to outline the anomaly with contrast media, especially barium, are unwise since this almost always overflows from the upper pouch into the lungs. Since the type 3b anomaly (Fig. 1) is present in over 80 per cent of all cases, it should usually be assumed that this is the condition involved and the treatment given should be on that assumption.

There are three conditions presented by any of these anomalies which must be met if the baby is to be saved. The secretions from mouth and nose, which cannot be swallowed, must be prevented from overflowing into the trachea; gastric contents must be prevented from passing upward through the esophagus into the lung through the fistula; and provision must be made for feeding. Perhaps because the anomaly usually goes unrecognized until repeated attempts at feeding have failed, the feeding problem has often been considered of first importance. Yet it is obviously not the most immediate consideration, since well-nourished newborn infants can be maintained for considerable periods by carefully administered parenteral fluids. There is, in fact, a report of a baby with the usual type of atresia and tracheo-esophageal fistula, which survived for thirty-seven days without feeding.[22] Almost always, however, these babies, when untreated, die much sooner than this as a result of respiratory failure due to flooding of the lungs with mucus. This symptom, indeed, is usually the first to appear, and should lead the alert pediatrician or obstetrician to suspect the condition before feeding is attempted. It can be treated palliatively, sometimes with success, by maintaining a head-down position and by frequent aspiration of the

pharynx, but any procedure designed to achieve permanent relief must provide for drainage from the mouth, through the upper esophagus, and it seems desirable that the first procedure should do so.

Regurgitation from the stomach through a tracheo-esophageal fistula becomes important only when a procedure to permit feeding is carried out. A long and uniformly dismal record of fatalities following gastros-

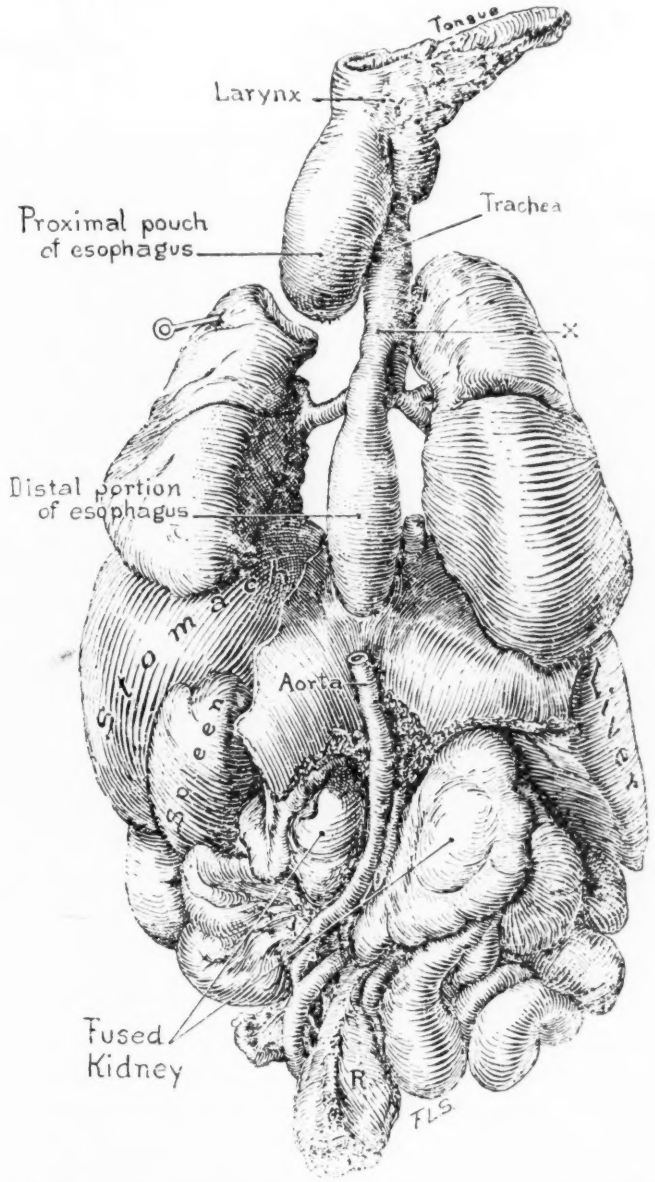
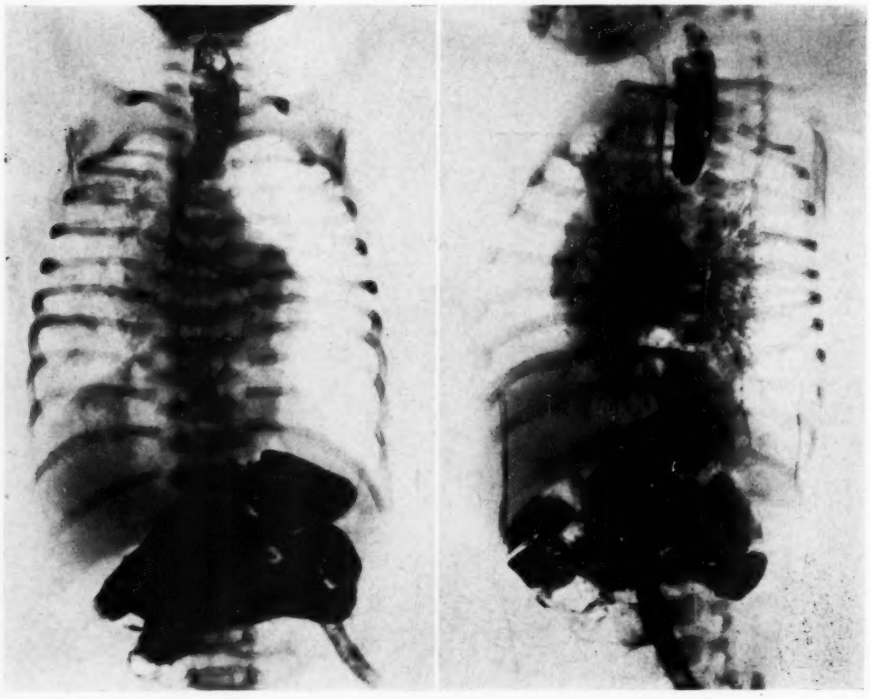


Fig. 1.—A drawing of the viscera removed at autopsy, viewed from behind, to show a typical anomaly of the commonest type (type 3b). The pharynx connects with a blind upper pouch which ends somewhat above the level of the tracheal bifurcation. The lower esophageal segment communicates directly with the posterior wall of the trachea at the bifurcation. Shown also is an incidental renal anomaly. (From Plass.[7])

tomy alone attests the fact that drowning by feeding always results unless the communication between stomach and trachea is closed, or unless the anomaly is one in which a fistula is not present (type 2 and type 3a). The observation that an opening between trachea and lower esophagus usually results in the stomach becoming filled with air has led to an assumption (Vogt[15]) that absence of gastric distension could be used to differentiate anomalies which lack this opening (types 2 and 3a) from those which have it (types 3b and 3c). This has proved to be false, as emphasized by Haight and Towsley[40] and demonstrated in this series (Fig. 2). Because types 3b and 3c constitute over 80



A. *B.*

Fig. 2.—Roentgenograms made after injecting lipiodal through a gastrostomy tube. The anomaly has been outlined by regurgitation of the oil upward through the tracheo-esophageal fistula into the lungs, and into the upper esophageal pouch. This picture was made in a living baby (Case 16) and illustrates not only the usual anomaly, but also the ease with which gastrostomy feedings fill the upper esophagus and respiratory tract. Since gastrostomy, without other procedure, was done on the false assumption that no fistula was present because the child at no time showed gastric distention, the picture also demonstrates the fallacy of that reasoning.

per cent of all cases, the presence of a fistula between trachea and lower segment must be assumed to be present in all cases, and it must be eliminated before any procedure to provide for feeding is done. Once the first two conditions have been met the problem of feeding becomes simple.

These basic principles have been slow to emerge. The obvious failure of gastrostomy led first to the hope that by jejunal feeding, regurgitation could be avoided, but it was found that jejunostomy was not only

an unsatisfactory method of feeding but also that material soon found its way back into the stomach. It has seldom been used.[2, 25] Richter[4] was the first to attempt a direct attack on the fistula in the mediastinum, but although suggestions for similar procedures were made by Lilienthal in 1926[14] and Iglauer in 1934,[27] as recently as 1936 Heatley,[30] considered that an intrathoracic approach presented "insurmountable practical difficulties." As a result, attempts were made to close the abdominal esophagus by ligation[21, 24, 29, 40] (Case 2, this series). Failure followed cutting through of the ligature in those infants who survived complications related to the untreated upper pouch. A more nearly successful approach, consisted in establishing drainage of the lower segment by transection of the stomach with establishment of an upper tracheoesophagogastric fistula, and a separate lower gastric opening for feeding. Variations of this procedure were reported in 1936 by Heatley[30] and Leven,[31] both of whom discounted the problem of the upper pouch, and each of whom reported two patients who survived for much longer periods than any previous ones. Similar procedures were less successful, however, in subsequent cases reported by Rosenthal,[32] Gamble,[34] and Lanman.[36]

The most recent procedure predicated upon avoiding a direct thoracic approach is that of Carter.[38] He recognized the primary necessity of draining the upper pouch by first establishing a cervical esophagostomy through a cervical approach, then solved the problem of feeding without regurgitation by bringing a large part of the lower esophageal segment down into the abdomen and transplanting it together with the fundus of the stomach under the skin of the anterior chest. This procedure meets all three conditions, but although the patient survived over two months, death finally resulted from a pulmonary complication, perhaps related to the persistent presence of a blind esophageal pouch connecting with the trachea. A theoretical objection to it also is the fact that in types 3a and 3c the upper segment could not be detached from the trachea without entering the chest.

Meanwhile an increasing number of intrathoracic procedures were being carried out. Following Iglauer's suggestion, Mixter[28] began approaching the anomaly directly through the right posterior mediastinum with the intention of establishing an esophagostomy for feeding by implantation of the lower segment in the back following division and ligation of the fistula, and draining the upper pouch by bringing it out in the back, or, later, in the neck. As reported by Lanman,[36] three of the infants so treated survived for relatively long periods, but all required abdominal gastrostomies, following retraction and closure of the opening in the back. In 1941, Leven[39] reported the first operation to result in long survival, and at almost the same time Ladd[42] independently worked out an essentially identical procedure which was equally successful. These patients, now over 4 years old, and several

others operated upon since that time by the same surgeons, are still living. A method differing mainly in the sequence of procedures has also been successful in three of the cases reported here.

By this technique drainage of the upper pouch is accomplished by cervical esophagostomy, regurgitation through the fistula is prevented by ligation and division of the tracheal communication in the mediastinum, and feeding is maintained by gastrostomy. Leven performed the last procedure first, thus risking the danger of regurgitation in spite of special precautions to avoid it. He next ligated the fistula and last of all brought out the upper pouch in the neck. Ladd carried out a mediastinal ligation first and followed with a gastrostomy after a few days. He also brought out the upper pouch as a third procedure, through a cervical approach. Both methods have the disadvantage, then, of requiring constant attention to the pharyngeal secretions during the most critical period, and may lead to late fatality if a fistula between the upper pouch and trachea is overlooked at the time of mediastinal exploration, since this cannot be corrected through a cervical approach. The procedure described here combines the cervical esophagostomy with the procedure of ligation and division of the fistula in the mediastinum, gastrostomy being delayed until healing of the mediastinum is firm. It has the advantage of being performable even after an attempt to obtain a direct anastomosis has proved impractical, and has been proved by experience to be feasible in the presence of a fistula between the trachea and upper pouch. In addition, the danger of aspiration of pharyngeal secretions is eliminated almost from the start.

It has always been obvious that the theoretical ideal would be a direct anastomosis, but attempts have usually failed because of the technical difficulties of holding together structures so small, so friable and frequently so disproportionate in size. The first reported attempt, recorded by Shaw[35] in 1939, ended in failure typical of other unsuccessful attempts later reported by Lanman,[36] Haight and Towsley,[40] Ladd,[42] and in this series. Separation of the anastomosis and mediastinal or pleural infection usually occurs. With increasing experience, however, a few patients have survived, some of them without leakage or stricture. The sole survivor in this series, however, developed both of these complications yet at the time of this communication appears to be doing well. Because the tedious and technically awkward process of building an anterior skin-lined tube to replace the esophagus is avoided, it has great advantages over any other procedure. It is desirable, then, to attempt a direct anastomosis in every case, although in many it will be found impossible to accomplish with even a reasonable hope of success. In these cases it seems best to abandon the attempt and carry out the procedure described here.

In Table I are summarized 153 operative cases including nineteen reported here for the first time. These operations have been carried

TABLE I

A SUMMARY OF THE OPERATIVE PROCEDURES IN 153 REPORTED CASES

	BRENNEMANN,[2, 6] 1913	RICHTER,[4] 1913	HIRSCH,[10] 1921	WEISS,[13] 1923	LILIENTHAL,[14] 1926	VOGT,[15] 1929	ROSENTHAL & HIMMELSTEIN,[21] 1932	BOHRER,[19] 1932	TUCKER & PENDERGRASS,[24] 1933	MATHIEU & GOLDSMITH,[22] 1933	STRONG & CUMMINGS,[25] 1934	MC CLELLAN & ELTERICH,[26] 1934	GAGE & OCHSNER,[29] 1936	HEATLEY,[30] 1936	LEVEN,[31] 1936	ROSENTHAL,[32] 1937	GAMBLE,[34] 1938	SHAW,[35] 1939	LANMAN,[36] 1940	LEVEN,[39] 1941	CARTER,[38] 1941	HAIGHT & TOWSLEY,[40] 1943	SINGLETON & KNIGHT,[41] 1944	LADD & GROSS,[42, 43] 1944	HUMPHREYS, 1944	TOTAL
Gastrostomy only	9		2	3	1	5	3	1		1		1				1			3			2	1		3	36
Jejunostomy only	2										1															3
Gastrostomy with ligation of esophagus							1		1				1									1			1	5
Transection of stomach														2	2	1	1		2							8
Cervical esophagostomy; transplantation of cardia and lower segment																					1					1
Ligation of fistula in mediastinum																			8				1			9
Mediastinal ligation and gastrostomy		2																	1			2			2	7
Mediastinal ligation and transplantation of lower segment																			5							5
Mediastinal ligation, cervical esophagostomy and gastrostomy																			3	5			1	28	6	43
Direct anastomosis																		1	5			13	1	6	6	32
Others																			1			2			1	4
Total	11	2	2	3	1	5	4	1	1	1	1	1	1	2	2	2	1	1	28	5	1	20	4	34	19	153

out by many different surgeons and often reported by pediatricians or pathologists, rather than by the surgeons who performed them, so that the details are not always available. Undoubtedly this list does not include all the operations which have been performed for this condition, especially in the first category, gastrostomy. Table I emphasizes, however, the fact that whereas isolated or small groups of cases were the rule up to five years ago, larger series are now being reported and that in those hospitals where experience has accumulated, a greater variety of procedures have been tried with a consequent improvement in results.

The same tendency is shown in the twenty-seven cases of atresia reported here for the first time (Table II). These cover a twenty-year period in Babies Hospital, but during the first fifteen years of this time only eleven patients were seen and only three were operated upon. Unquestionably this changing record does not represent an altered incidence in the condition, but rather an increasing awareness of its existence on the part of pediatricians and of willingness to attempt its correction on the part of surgeons.

Two of the three patients operated upon during the first fifteen-year period had simple gastrostomies which resulted in death one and six days after operation through aspiration of the feeding. The third also had a gastrostomy and ligation of the abdominal esophagus, also resulting fatally. The sixteen recent cases have all been direct attacks upon the fistula in the chest except for one (Case 16). In this case the anomaly was mistakenly thought to be type 2 (atresia without fistula) because the infant showed no air in the stomach eight days after birth. Gastrostomy only was done with the usual death by aspiration of feeding (Fig. 2). In two patients (Case 12 and Case 19) approach was through the pleural cavity; the remaining 13 were all through the mediastinum. In two other patients (Cases 12 and 13) the procedure consisted merely of ligation of the fistula in the chest and gastrostomy. When carried out transpleurally it resulted in death from respiratory failure three days later; when carried out in the mediastinum the infant survived fourteen days, dying then because of the cutting through of the ligature and re-establishment of the fistula with consequent aspiration of feeding. This outcome followed a similar procedure in Ladd's series.[42] The remainder were all undertaken with the intention of carrying out a direct anastomosis and in six this was done. In the other seven cases either no attempt was made because it was apparent that the interval between the segments was too great, or an unsuccessful attempt was made and abandoned in favor of the more conservative procedure of ligation and cervical esophagostomy. The latter procedure has been successful in three of the seven cases, whereas only one of the direct anastomoses has succeeded.

The anomalies were of the characteristic type 3b (Fig. 1) in twenty-two of the twenty-seven cases (82 per cent). This frequency is similar

TABLE II

ANALYSIS OF 27 CASES

CASE	DATE OF BIRTH	CONDITION ON ADMISSION	OPERATIONS		RESULT		DIAGNOSIS MADE BY	TYPE OF ANOMALY	OTHER ANOMALIES
			TYPE	DAYS AFTER BIRTH	CAUSE OF DEATH	DAYS AFTER BIRTH			
1. L. S.	4/ 8/23	Full term, good	None		Bronchopneumonia	4	Autopsy	3b	Meckel's diverticulum, supernumerary pancreas
2. P. O.[1]	7/25/23	Full term, good	Gastrostomy and intraperitoneal ligation of esophagus	8	Pulmonary abscesses, general peritonitis	14 6 P.O.	Contrast x-ray	3b	None
3. B. S.	8/ 3/24	Advanced pneumonia	None		Pneumonia	2	Passage of catheter	3b	None
4. A. O.	1/16/27	1 mo. premature, emaciated	None		Pulmonary congestion	14	Passage of catheter	2 (atresia only)	Horseshoe kidney, meningocele
5. B. S.	4/23/28	1 mo. premature	None		Bismuth pneumonia	6	Bismuth x-ray	2 (atresia only)	Mongolism (no autopsy)
6. J. C.	11/ 8/28	Full term, pneumonia	None		Sepsis with multiple abscesses, pneumonia	18	Contrast x-ray	3b	Supernumerary spleen
7. G. C.[3]	6/15/30	Full term	Gastrostomy only	6	Pneumonia and abscesses	16 6 P.O.	Barium x-ray	3b	None
8. F. T.	6/30/30	3 weeks premature, jaundiced	None		(?) Pneumonia	6	Barium x-ray	2 (atresia only)	None ? (no autopsy)
9. M. W.[3]	5/15/31	Full term, good	Gastrostomy only	6	Drowned by feeding	7 1 P.O.	Barium x-ray	3b	None
10. B. J.	7/26/36	Full term, pneumonia	None		Barium pneumonia	4	Barium x-ray	3b	None

TABLE II—CONT'D

11. M. P.	5/22/38	Full term	None		Barium pneumonia	11	Barium x-ray	3b	Congenital heart, I.V. septal defect
12. A. E.[2]	6/14/41	Full term, good	Transpleural intrathoracic ligation and gastrostomy	4	Respiratory failure	7 3 P.O.	Barium x-ray	3b	Stricture of ureter, hydronephrosis
13. B. B.[4]	7/18/41	Full term, jaundiced	Mediastinal ligation, gastrostomy	4 8	Drowned by feeding	23 14 P.O.	Barium x-ray	3b	Left superior vena cava
14. S. E.[4]	10/29/41	Full term, good	Mediastinal anastomosis	5	(?) Pneumonia	7 2 P.O.	Barium x-ray	3b	None ? (no autopsy)
15. K. D.[4]	12/ 9/41	2 wk. premature	Mediastinal anastomosis	1	Pneumonia, mediastinal abscess	4 3 P.O.	Contrast x-ray	3b	None
16. M. C.[4]	4/ 9/42	Full term, pneumonia	Gastrostomy only (fistula not recognized)	9	Aspiration pneumonia	16 7 P.O.	Lipiodal x-ray	3b	None ? (no autopsy)
17. B. B.[4]	6/ 6/42	1 mo. premature, jaundiced	Mediastinal anastomosis	3	Pneumothorax following opening of anastomosis	5 2 P.O.	Contrast x-ray	3b	None
18. H. D.[5]	9/13/42	1 mo. premature, jaundiced	Mediastinal anastomosis, drainage of empyema	5 10	Empyema following opening of anastomosis	15 10 P.O.	Lipiodal x-ray	3b	Horseshoe kidney, hemivertebra; supernumerary rib
19. J. G.[5]	9/22/42	Full term	Transpleural anastomosis	2	Respiratory failure	4 2 P.O.	Barium x-ray	3b	None ? (no autopsy)
20. M. M.[5]	11/19/42	Full term, 4 lb.	Mediastinal ligation and division, cervical stoma; gastrostomy	4 9	Living and well	407 1/1/44	Passage of catheter	3b	Thoracic hemivertebra
21. D. F.[5]	12/ 6/42	Full term, good	Mediastinal ligation and division, cervical stoma	1	Hemorrhage into trachea from fistula	5 4 P.O.	Passage of catheter	3b	Calcium concretions in kidneys
22. D. H.[5]	12/25/42	Full term, good	Mediastinal ligation and division, cervical stoma; gastrostomy; revision of stoma	4 9 54	Respiratory failure, aspiration of mucus	65 61 P.O.	Contrast x-ray	3c	Horseshoe kidney, thoracic hemivertebrae; supernumerary ribs

CASE	DATE OF BIRTH	CONDITION ON ADMISSION	OPERATIONS		RESULT		DIAGNOSIS MADE BY	TYPE OF ANOMALY	OTHER ANOMALIES
			TYPE	DAYS AFTER BIRTH	CAUSE OF DEATH	DAYS AFTER BIRTH			
23. S. K.[5]	3/19/43	Full term, good	Mediastinal ligation and division, cervical stoma; gastrostomy; revision of stoma	2 7 163	Living and well	287 1/1/44	Passage of catheter	3b	Congenital heart? (living)
24. G. T.[5]	7/29/43	Full term, good	Mediastinal ligation and division, cervical stoma; gastrostomy	10 15	Living and well	155 1/1/44	Passage of catheter	3b	None ? (living)
25. P. R.[5]	8/26/43	1 mo. premature 5 lb.	Mediastinal exploration, cervical stoma	4	Pneumonia	7 3 P.O.	Passage of catheter	2	None
26. S. W.[5]	9/ 1/43	Full term, good	Mediastinal anastomosis	6	Living and well	122 1/1/44	Passage of catheter	3b	None ? (living)
27. McG.[6]	10/26/43	Premature	Mediastinal ligation and division, cervical stoma; gastrostomy	1 6	Respiratory failure	7 6 P.O.	Passage of catheter	3b	Imperforate anus, multiple hemivertebrae, congenital heart, persistent left superior vena cava, malformation of lung, anomalies of spleen and pancreas, bicornuate uterus

[1]Operation by Dr. Bolling.
[2]Operation by Dr. E. J. Donovan.
[3]Operation by Dr. F. W. Solley.
[4]Operation by Dr. W. G. Heeks.
[5]Operation by Dr. G. H. Humphreys.
[6]Operation by Dr. J. McDonald.

Fig. 3.—Diagrams to show various types of procedure. Upper line: Primarily abdominal procedures. *A*, Gastrostomy, *B*, gastrostomy and abdominal ligation of esophagus, *C*, transection of stomach, *D*, cervical esophagostomy and transplantation of cardia. Lower line: Primarily thoracic procedures. *E*, Mediastinal ligation and gastrostomy, *F*, mediastinal ligation and transplantation of lower segment (cervical esophagostomy), *G*, mediastinal ligation, cervical esophagostomy, and gastrostomy, *H*, direct anastomosis.

to that in most reported series. There were four cases of atresia without fistula, only one patient being operated upon. There was one instance (Case 22) in which fistulas were present between both segments and the trachea (type 3c). This patient is of particular interest since the condition demonstrates the feasibility of repairing an opening in the membranous portion of the upper trachea, as well as ligating a lower tracheal fistula, a procedure which would not be possible if the attempt had been made to carry out the cervical esophagostomy without opening the chest as recommended by Leven and Ladd. The baby did well for two months, but the attachment of the upper segment to the skin of the neck had been made under too much tension and subsequently retracted. When the cervical stoma closed, aspiration of pharyngeal mucus recurred and proved fatal.

Contrary to common belief the associated anomalies are relatively infrequent and unimportant. They were present in only ten of the twenty-seven cases. In only one case (Case 27) were they of sufficient severity to influence the outcome. They were present in two of the four surviving patients, one of whom had hemivertebrae and the other a congenital heart murmur without cyanosis. The argument that the babies presenting this anomaly are congenitally defective in other ways and therefore not worth saving does not appear, then, to be valid.

PROCEDURE

The earlier operations were carried out under various types of anesthesia, but the last ten have been done using only a little novocain in the skin and thereafter no anesthesia at all. An anesthetist has always been present to administer oxygen under positive pressure from time to time and to keep the nasopharynx clear of mucus by frequent aspiration. It is probable that the avoidance of general anesthesia is an important factor in these babies' survival as is shown by the fact that all of the babies in this series have survived for at least forty-eight hours after operation, in contrast to the frequent deaths of shock during or immediately after operation in cases reported from other hospitals where general anesthesia has been used.

The baby is placed on his abdomen lying across a hot-water bag about one-half full of warm water. The thorax is tilted slightly to the right by means of a folded towel and the head is turned to the right. A small, tightly fitting mask is used for the occasional administration of oxygen under slight pressure, but for much of the time the baby breathes room air. The arms and legs are held in the position illustrated (Fig. 4) with carefully padded restraints.

A curved incision is made beginning about 1 cm. lateral to the spine over the second rib, and passing downward parallel to the spine over the third and fourth ribs and thence laterally just medial to the vertebral border of the scapula, crossing the fifth rib at an oblique angle and end-

ing over the sixth rib (Fig. 5*A*). The trapezius and rhomboid muscles are divided across their fibers in the same plane as the skin incision. Occasionally some of the upper fibers of the latissimus dorsi also require division. The attachments of the paraspinal muscles to the second, third, and fourth ribs are then divided and a 2 cm. segment of the fifth rib is resected subperiosteally. Great care is necessary to avoid puncturing the pleura when the periosteum is separated from the inner surface of the rib. By resecting a segment of rib of this length, however, it is possible to expose the plane between pleura and chest wall without great difficulty.

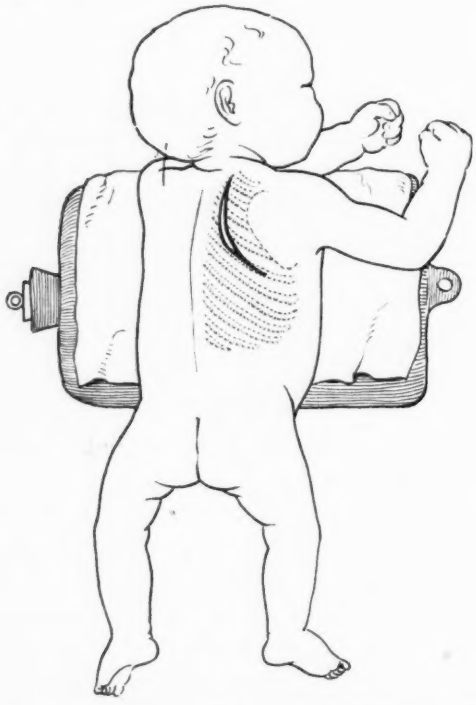


Fig. 4.—A drawing to show position of infant on operating table as viewed from above. Restraints are used on forearms and lower legs to maintain this position. The infant is placed across a warm hot-water bottle not only to maintain warmth but also to flex the spine slightly to the left. Not shown is a small, folded towel under the right shoulder to maintain rotation of the thorax. The curved incision around the right scapula is indicated.

The pleura is then gently stripped away from the neck of the fifth rib and the dissection carried upward in the same plane under the fourth rib, the neck of which is divided after ligating the intercostal muscle bundle. In a similar fashion the intercostal muscle bundles and necks of the third and second ribs are divided (Fig. 5*B*). The pleura is then lifted away from the necks of the ribs as far forward as their articulations with the spine, at which point the azygos vein comes into view (Fig. 5*C*). This vein is ligated and divided at the point where it arches forward across the mediastinum. When this has been done the posterior mediastinal pleura can be gently pushed forward away from

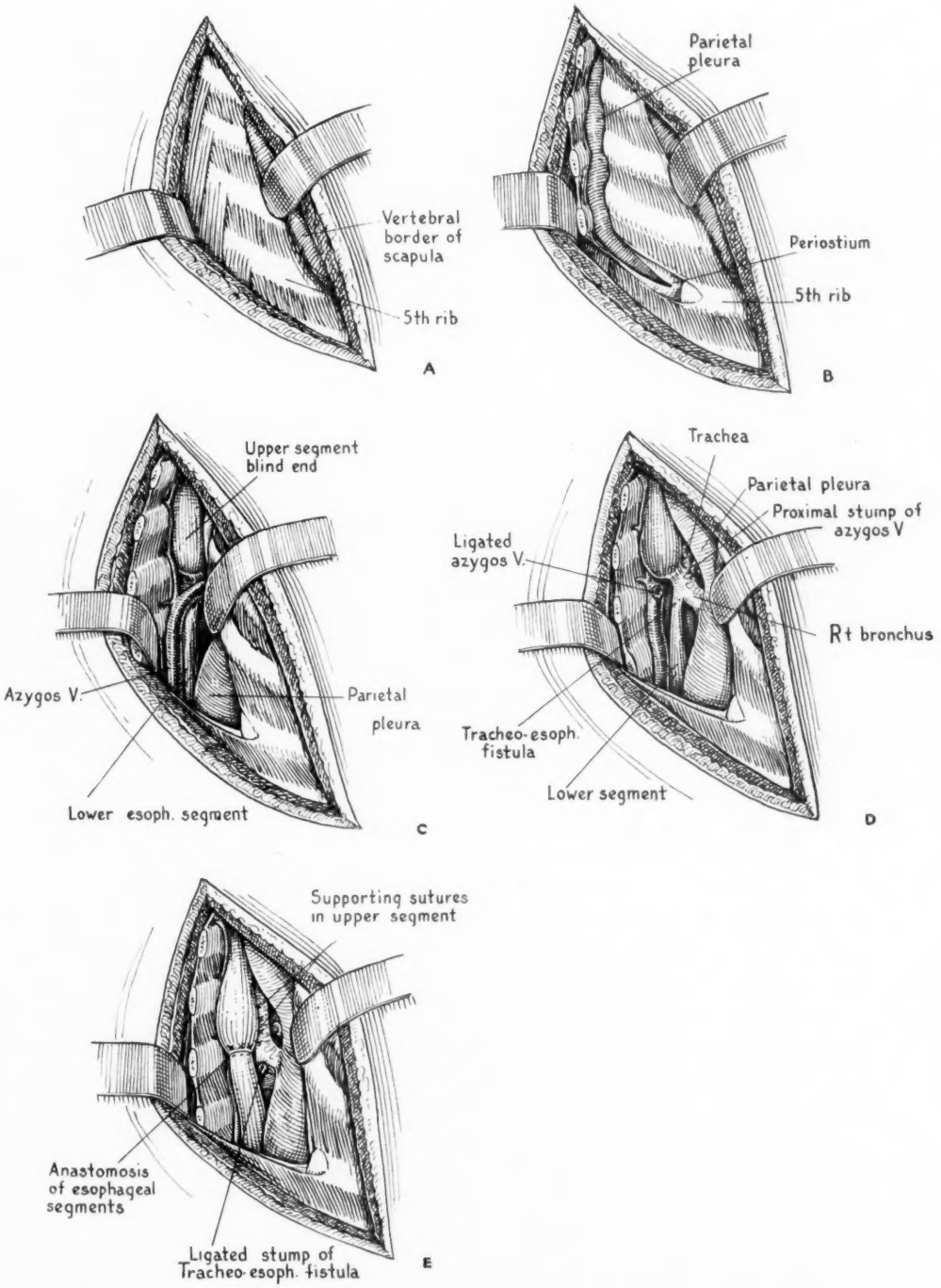


Fig. 5.—Steps in the operative procedure: *A*, Exposure of the upper five ribs following division of muscles and retraction of scapula. *B*, Showing extent of rib resections and incision through the fifth rib bed to expose the underlying pleura. *C*, The pleura has been retracted laterally and forward away from the necks of the ribs to expose the azygos vein. The upper pouch is barely visible; the lower segment is not yet exposed. *D*, Ligation and division of the azygos vein permits further retraction of the pleura exposing the anomaly. *E*, A direct anastomosis has been accomplished by drawing the upper pouch downward and anastomosing it to the lower segment following division and ligation of the tracheo-esophageal fistula.

the esophagus and trachea. The fingerlike blind end of the upper pouch is usually readily identified. If it extends fairly deep into the chest no traction is needed to keep it within view. But if it is unusually short it may disappear almost completely into the neck when the patient attempts to swallow. In this case it is desirable to pass a traction suture through its tip so that it may be gently drawn downward into the operative field whenever desired. Immediately anterior to the blind pouch lies the main column of the trachea and this can be followed downward to its bifurcation at approximately the level of the ligated azygos vein. At this point the lower esophageal segment is typically found to emerge as a small stalk, either from the posterior membranous portion of the trachea or from the bifurcation itself. Occasionally it has been described as coming from one of the primary bronchi, although that has not been the case in any of the patients reported here. In some instances there is no tracheo-esophageal communication, in which case the lower esophageal segment may not be apparent in the operative field (as in Case 25).

After clarifying the nature of the anomaly, a decision must be made as to its treatment. If a tracheo-esophageal fistula is present, correction of this must be the first step. This is accomplished by ligating the upper end of the lower esophageal segment as close to its entrance into the trachea as possible. A second ligature is then placed a millimeter or two below the first and the esophagus is divided between them. Attempts to invert either end of the esophagus are usually ineffective and have proved to be unnecessary. If it is thought that an attempt to perform a direct anastomosis is justifiable, it is better not to place the second ligature, but rather to insert a stitch through the muscularis of the lower segment and then cut across the lumen without attempting to keep it closed. Clamping the esophagus is undesirable since it crushes the tissue and may lead to reopening of the fistula.

When the lower esophageal segment has been separated from its attachment to the trachea, the upper pouch is dissected free of its attachments, carrying the dissection well upward into the base of the neck. Ordinarily these attachments are very loose and the dissection is easily accomplished, but in one instance (Case 22) the upper pouch was found to be very adherent to the membranous portion of the trachea so that the latter was entered in separating the two structures. It is probable that an actual fistula was present at this point. In this case the trachea was repaired by continuous suture without subsequent leakage into the mediastinum. When the upper pouch is free, it may be drawn down into apposition with the cut end of the lower segment and an anastomosis performed by making a small opening through all layers of the pouch, suturing this opening to that of the lower segment with interrupted mattress sutures, and reinforcing the suture line by draw-

ing the outer surface of the upper pouch downward over the anastomosis (Fig. 5*E*). This procedure is a tedious one and if the gap between the two segments is more than 1 cm. before the anastomosis is begun, it will usually be found that the first vigorous respiratory effort on the part of the infant causes a disruption of the anastomosis. Under these circumstances it should not be attempted.

In order to prevent pursing of the esophagus at the point of anastomosis it has been found convenient to slip a fairly stiff rubber catheter into the esophagus, preferably inserting its base into the upper pouch and pushing it upward into the mouth, after which the tip can be inserted into the lower segment. Its presence will ensure a lumen of at least the diameter of the catheter and small gaps in the anastomosis will be more easily detected than if the esophagus is left empty. In the earlier anastomoses the catheter was frequently left in place after operation in the hope that it might be utilized for gavage feeding. This practice is now considered undesirable since the baby is stimulated to nurse constantly on the tube in the pharynx, thus increasing its oral secretions and putting an unnecessary strain on the anastomosis. If the anastomosis is satisfactory, normal swallowing will be established within ten days; if leakage becomes apparent, a gastrostomy is necessary.

If it has been determined that anastomosis is not feasible, either because the length of the gap is too great or because the lumen of the lower segment is too small, the lower segment may be ligated near its cut end and dropped back into the mediastinum. A finger is then passed upward along the posterior surface of the trachea into the base of the neck where it can easily feel the subclavian vessels and the great vessels of the neck. The towels which drape the patient are moved slightly to expose the supraclavicular region and the neck in the region of the suprasternal notch. In some instances it has been found simpler to make an incision lateral to the sternomastoid muscle, but it is more desirable to place it between that muscle and the trachea just above the sternum. Through this incision a blunt clamp is passed, guiding its progress with the finger tip in the wound, into the upper posterior mediastinum. Here it grasps the traction suture on the tip of the esophageal pouch so that the latter is drawn upward and forward through the neck incision when the clamp is withdrawn (Fig. 6).

If it is felt that contamination of the mediastinum from the trachea or upper esophageal pouch has been considerable, it may be considered desirable to dust the exposed mediastinal tissues with sulfadiazine powder. This procedure, however, has resulted in very high blood sulfadiazine levels for several days in some of the patients in which it was carried out. If a direct anastomosis has been done, it is probably best to drain the posterior mediastinum as more or less leakage is to

be expected. It is usually not practical to attempt to close the intercostal muscles, although in some cases it is desirable to do so, especially if the pleura has been inadvertently entered. The wound is closed around the drain, if present, by interrupted sutures through the rhomboid and trapezius muscles and the skin is closed with interrupted sutures. Both silk and catgut have been used in these procedures; no conspicuous difference has been noted in relation to the suture material.

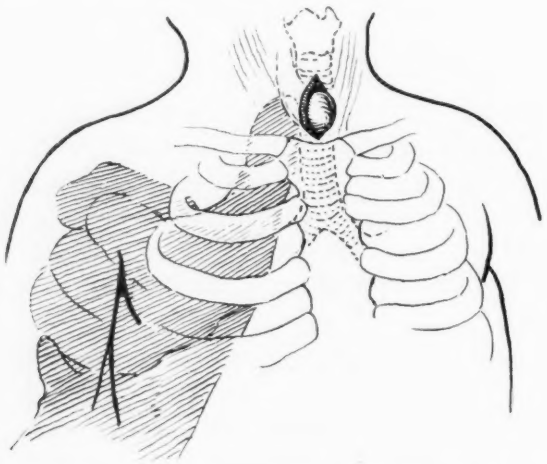


Fig. 6.—A diagram to show the method by which the upper esophageal pouch is brought out in the neck after it has been dissected free in the mediastinum, in those cases in which anastomosis is not possible.

After the posterior wound has been closed and a dressing applied, the baby is turned on its back and redraped to expose the wound in the neck through which the pouch has been drawn. An opening is made in the end of the pouch in the direction of the muscular fibers corresponding in length to the skin incision. If there is any tension or tendency for the pouch to retract into the neck, it is advisable to place several deep sutures between the muscularis of the pouch and the deep fascia or sternomastoid muscle in the neck. The skin and mucous membrane are then approximated with interrupted sutures, preferably very fine chromic catgut so that removal will not be necessary. The patient is then returned to the ward in an oxygen tent or closed bed in which a high oxygen tension can be maintained. Moderate external heat is desirable in most cases and the child should be kept in slight Trendelenburg position, lying on his back or right side.

POSTOPERATIVE CARE

It is essential to have a suction apparatus constantly at the bedside and to keep the mouth and pharynx clear of mucus which tends to accumulate, especially during the first few days while the cervical stoma is closed due to postoperative edema. As soon as this edema subsides,

and drainage from the neck is established, the danger of sudden suffocation by aspiration of saliva is much less but not entirely absent. Since no provision is made for feeding on the first procedure, it is necessary to maintain fluids parenterally. Infusions or transfusions may be desirable, but the main reliance must be on hypodermoclyses of glucose, saline, and amigen. At the same time it is necessary to guard against overhydration and nitrogen retention which may occur because of depressed renal function during the first week or more.

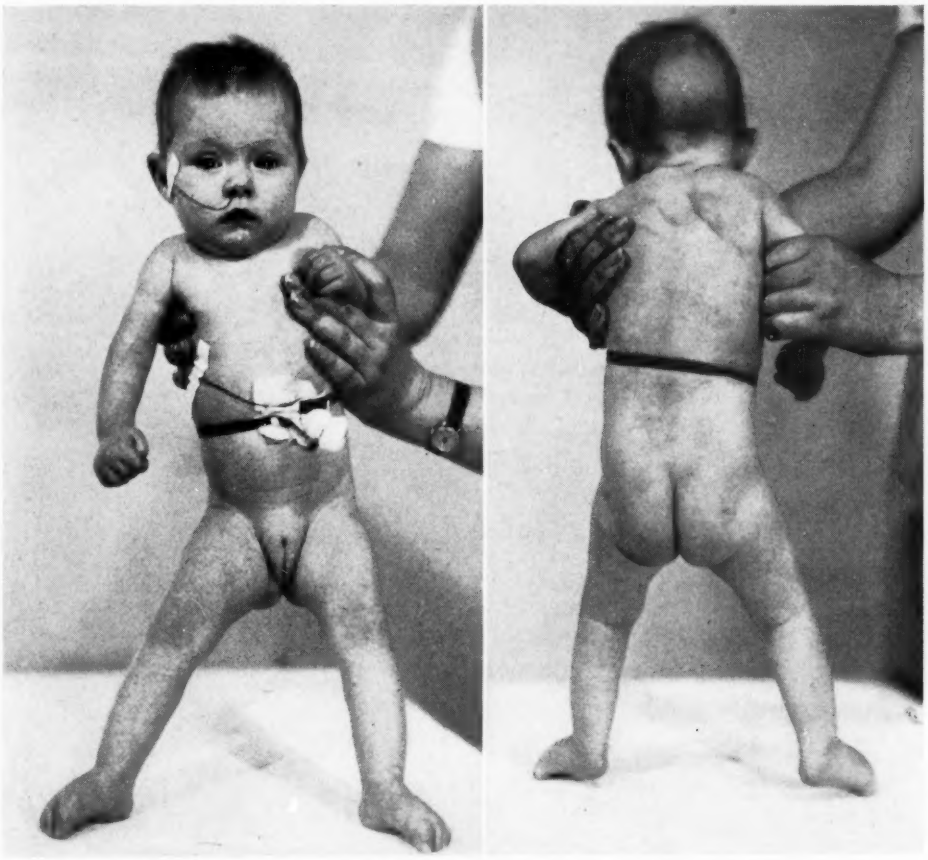


Fig. 7.—Patient (Case 26) four months after primary anastomosis, followed by gastrostomy. A string is being kept in the esophagus emerging from nose and gastrostomy in order to maintain occasional dilatations. A short tube is also still present in the gastrostomy opening, but the infant takes all her feedings by mouth. The well-healed right thoracic scar is evident.

Gastrostomy for feeding purposes has usually been delayed until the fourth or fifth day after the first procedure in order to allow sufficient healing of the upper end of the lower esophageal segment so that regurgitation into the wound may be avoided, and also because at the time of the first procedure many of these children are suffering from pneumonia which should be given time to resolve before subjecting them to a second.

When direct anastomosis has been performed, it is considered best not to try oral feedings for at least one week. Saliva and nasal mucus, however, will be swallowed continually and if a leak or separation in the anastomosis is present this material will accumulate in the mediastinum or pleura unless it is allowed to escape through a drainage tract. This leakage, with consequent infection in pleura or mediastinum, was responsible for the death of three patients of the six in whom anastomoses had been done. Two of the others died of respiratory complications too soon after the operation to know whether leakage would have occurred. The one surviving patient also showed profuse leakage of nasal and oral secretions through the drainage tract in the posterior mediastinum for a period of ten days. A gastrostomy for feeding purposes will, therefore, be necessary in many of the patients with direct anastomosis.

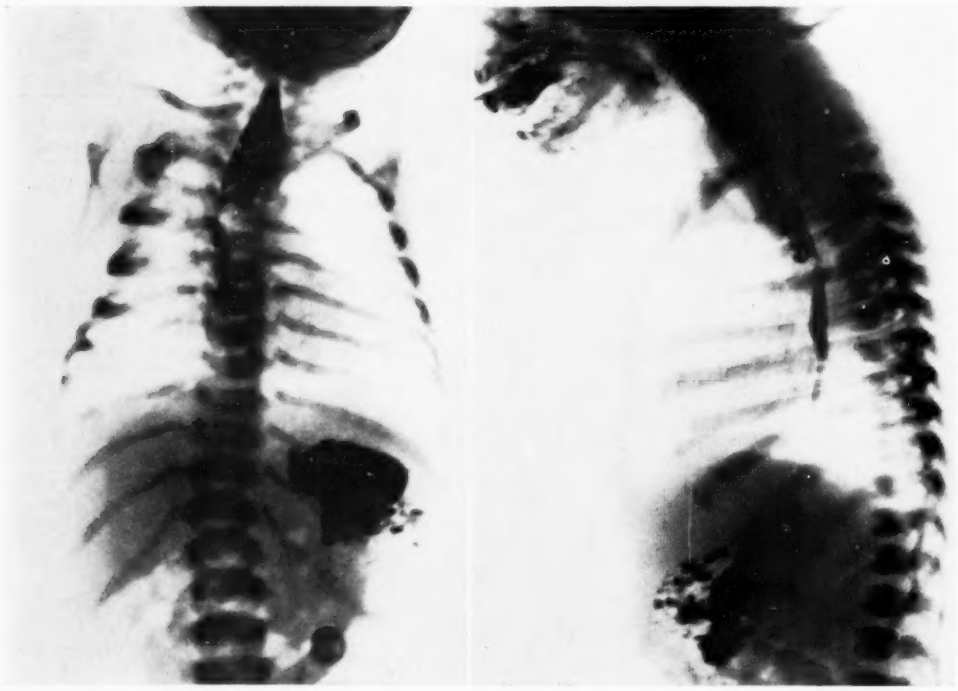


Fig. 8.—X-rays taken after swallowing of lipiodal one month after primary anastomosis, showing free passage of oil into the stomach, but an area of stenosis at the anastomotic site. This was later dilated.

The gastrostomies have all been performed in the anterior wall of the antrum of the stomach, using local anesthesia and inserting a catheter either by the Witzel technique or with multiple purse-string sutures. The operation is usually well borne and free of complications. Feeding through the gastrostomy is begun the day after operation and can be advanced rapidly from clear fluids to an evaporated milk formula in many small feedings. As soon as this is established, the babies who have succeeded in reaching this point usually gain quite rapidly and develop

without further complications. However, three months after the first operation one infant in this series died due to pulmonary complications secondary to retraction of the cervical pouch and reappearance of aspiration of mucus.

Those infants who survive after formation of a cervical stoma, closure of the fistula, and gastrostomy still present a considerable problem. Ultimately it will be necessary to form some type of external skin-lined tube on the anterior chest wall in order to connect the cervical stoma with the stomach. As yet no such procedure has been attempted since it has been felt that the multiple-stage operations would not only be more easily carried out, but also better borne, after the first year of life.

SUMMARY

The problem presented by infants born with atresia of the esophagus, usually associated with tracheo-esophageal fistula, has been discussed from the point of view of surgical care. It has been brought out that after a long period, during which the attitude was one of hopelessness, there has developed during the last decade a sufficiently concentrated experience so that a definite evolution of treatment has occurred which has finally resulted in the emergence of principles by which some, at least, of these babies can be saved. This evolution has been traced by an analysis of 134 operative cases reported by twenty-four authors during the last thirty years, to which have been added the nineteen operative cases among twenty-seven seen at the Babies Hospital during the past twenty years and not previously reported. Twenty-four babies have survived operation and are still living today (Table III.) Of these a direct anastomosis has been successful in eight. Sixteen have had the fistula divided in the mediastinum, the upper segment brought out in the neck, and a gastrostomy for feeding purposes. These present a considerable problem in reconstructive surgery.

TABLE III

ANALYSIS OF SURVIVING PATIENTS

	MEDIASTINAL LIGATION, CERVICAL STOMA, AND GASTROSTOMY		DIRECT ANASTOMOSIS	
	OPERATIONS	SURVIVALS	OPERATIONS	SURVIVALS
Leven	?	5		
Ladd and Gross	28	8	6	2
Haight and Towsley			13	5
Humphreys	6	3	6	1
Total	?	16	25	8

This record shows conclusively that these anomalies of the esophagus are not necessarily incompatible with life and that the most successful surgical approach to them lies in a direct attack upon the lesion in the mediastinum through a thoracic approach.

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THE TRANSFUSION OF MASSIVE VOLUMES OF CITRATED WHOLE BLOOD AND PLASMA IN MAN

Clinical Evidence of Its Safety

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RECENTLY, reports from the laboratories of Ivy and associates[1] and of Graham[2] have indicated that the liberal use of citrated blood and plasma may be hazardous, and they have warned against large transfusions in man. This warning is based upon experimental work performed on dogs in which they considered that citrate intoxication probably accounted for the death of the animals transfused.

At present, war casualties and the expanding scope of civilian surgery are often accompanied by a severe loss of blood. Such extensive blood loss must be replaced, preferably with blood, if fatalities from hemorrhage are to be prevented. Hemorrhage of extensive magnitude may necessitate the use of massive transfusions. If, however, the liberal use of citrated blood or plasma is in itself harmful, then other less toxic replacement fluids should be substituted.

During the past eighteen months we have had the opportunity to observe the effects of extensive blood loss and its replacement by large volumes of whole blood and plasma in fifty-three patients undergoing radical surgical operations. For the most part these patients were suffering from fairly advanced malignant disease. The clinical observations during and after the use of large transfusions constitute the basis for this report. Only patients who received 1,500 c.c. or more of blood and/or plasma continuously, exclusive of citrate volume, are included.

PRESENTATION OF DATA

The cases comprising this report have been classified in Table I according to whether the operation was performed on the chest, abdomen, or both and the extremities.

Table II shows the different volumes of blood and/or plasma administered, and the number of patients receiving these various amounts.

Table III is a detailed summary of the fifty-three patients presented. Red blood counts and hemoglobin determinations were made within

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TABLE I

TYPES OF OPERATIONS ON PATIENTS RECEIVING MASSIVE TRANSFUSIONS

OPERATION		NUMBER
1. Thoracic		16
(a) Chest wall	2	
(b) Intrathoracic	8	
(c) Thoraco-abdominal	6	
2. Abdominal		35
3. Extremities		2
Total		53

TABLE II

TOTAL VOLUME OF BLOOD AND/OR PLASMA ADMINISTERED*

AMOUNT	NUMBER
1500 to 2000	19
2000 to 2500	10
2500 to 3000	11
3000 to 4000	6
4000 to 5000	4
6000 to 7000	2
Total	52

*One patient received less than 1,500 c.c., but received 0.13 Gm. of citrate per kilogram of body weight in 150 minutes.

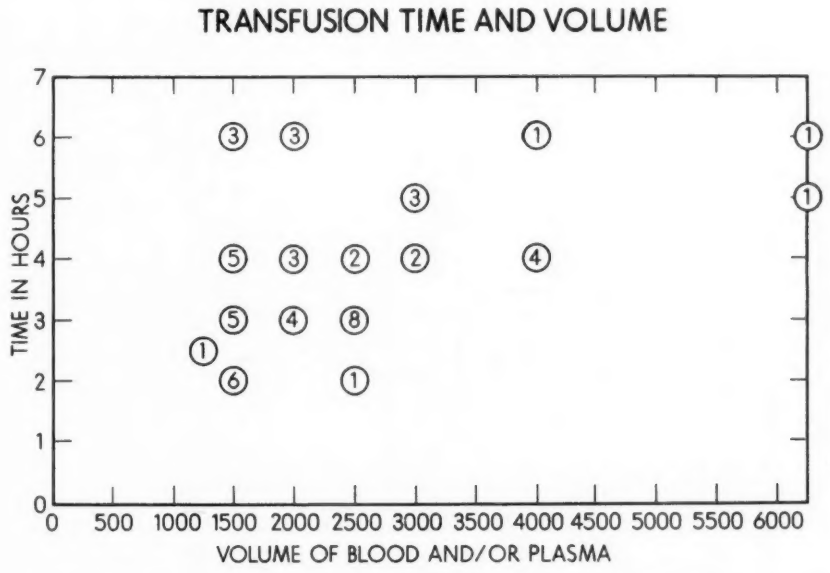

Fig. 1.—The chart shows the number of patients receiving various amounts of blood and/or plasma in given periods of time.

two to three days before operation. These blood studies were repeated twenty-four hours postoperatively in forty-eight patients and in two to three days in the remaining five patients.

As shown in Fig. 1, most patients received 1,500 to 2,500 c.c. of blood and/or plasma in a period of from two to six hours.

The amount of sodium citrate used as the anticoagulant in our whole blood transfusions was 2.5 Gm. for each 500 c.c., while our plasma con-

TABLE III

DETAILED INFORMATION ON 53 PATIENTS WHO RECEIVED MASSIVE TRANSFUSIONS OF BLOOD AND/OR PLASMA

CASE NO.	(KG.) WT.	DIAGNOSIS	OPERATION	BLOOD STUDIES				URINE OUTPUT (C.C.)		CITRATED BLOOD AND/OR PLASMA		GM. CITRATE USED IN TRANSFUSION
				PRE-OPERATIVE		POST-OPERATIVE						
				R.B.C.	HB.	R.B.C.	HB.	24 HR.	48 HR.	AMT. (C.C.)	TIME (HR.)	
			Chest Wall									
1. L. R.	57.0	Empyema	Extensive thoracoplasty	3.35	10.5	4.12	11.0	700	600	1500 B	1.5	7.5
2. G. S.	55.8	Empyema	Extensive thoracoplasty	4.23	14.0	3.90	14.0	300	800	1500 B	6	7.5
			Intrathoracic									
3. G. S.	55.8	Carcinoma right lung	Pneumonectomy	4.10	11.0	4.00	14.0	–	1100	1500 B	6	7.5
4. J. M.	94.7	Bronchiectasis	Left lower lobectomy	5.12	14.5	4.70	13.5	750	1700	1500 B	2.5	7.5
5. C. S.	76.3	Carcinoma, left lung	Pneumonectomy	5.70	17.2	5.20	15.2	800	970	1500 B	2	7.5
6. R. T.	104.0	Tumor, right lung	First stage lobectomy	4.50	14.5	3.90	12.5	1500	1900	2500 B	2.5	7.5
7. J. K.	75.9	Carcinoma, right lung	Pneumonectomy	4.50	12.6	5.05	16.5	300	–	2650 B	3	10.0
8. R. T.	104.0	Tumor, right lung	Right middle and lower lobectomy	4.50	14.8	3.80	13.8	–	1640	2700 B	2.5	12.5
9. M. H.	87.0	Tumor, left lung	Pneumonectomy	4.10	14.0	5.10	12.0	–	1020	2500 B	2.5	12.5
10. R. R.	60.2	Hemangioma, left lung	Pneumonectomy	7.20	23.0	5.05	15.5	700	1000	2400 P	2.5	16.0
			Thoraco-abdominal									
11. P. M.	92.0	Carcinoma of cardia	Radial resection and anastomosis	4.91	14.0	5.82	14.0	0	1370	1500 B	6	7.5
12. E. T.	71.0	Carcinoma of esophagus	Radical resection and anastomosis	3.78	13.0	4.00	13.0	0	445	1500 B	5	7.5
13. O. S.	52.0	Carcinoma of esophagus	Radical resection and anastomosis	4.93	14.5	5.12	15.5	100	1375	1500 B	4	7.5
14. G. S.	62.0	Carcinoma of stomach	Total gastrectomy	4.00	14.0	4.40	13.5	250	650	2000 B	6	10.0
15. L. B.	72.0	Carcinoma of esophagus	Radical resection and anastomosis	4.06	15.5	4.93	16.5		2000	2000 B	3.5	10.0
16. P. P.	50.0	Carcinoma of esophagus	Radical resection and anastomosis	4.57	14.0	4.80	12.6	400	1150	2000 B 600 P	6	14.0
17. E. M.	37.0	Retroperitoneal sarcoma	Excision of sarcoma	4.91	11.5	5.14	14.0	250	600	1000 B	2	5.0
			Abdominal									
18. M. W.	75.0	Carcinoma, common duct	Radical resection of small bowel	4.75	14.5	3.75	13.0	1810	225	1500 B	3	7.5
19. A. A.	45.0	Carcinoma of stomach	Radical resection of small bowel	4.51	13.0	4.54	11.5	600	1000	1500 B	3	7.5
20. C. B.	51.0	Carcinoma of cecum	Radical colectomy	4.14	14.0	4.34	14.5	300	1405	1500 B	2	7.5
21. C. J.	44.0	Recurrent regional enteritis	Radical resection of small bowel and colon	4.70	15.0	4.38	12.5	200	–	1500 B	2	7.5
22. B. H.	39.0	Carcinoma of colon	Radical resection of colon	3.85	10.5	3.05	9.0	0	0	1500 B	4	7.5

23. J. A.	60.0	Common duct stone	Cholecystectomy and drainage of common duct	4.50	12.0	4.50	14.0	500	600	1500 B	2	7.5
24. R. W.	45.0	Carcinoma of pancreas	Pancreatoduodenectomy	3.70	12.0	4.10	13.0	1675	1150	1500 B	3.5	7.5
25. Y. L.	60.0	Lymphoma of bowel	Radical resection bowel	4.00	10.0	4.20	13.0	250	500	1500 B	3	7.5
26. N. G.	65.0	Carcinoma of pancreas	Pancreatoduodenectomy	3.24	11.0	4.10	13.0	1090	890	1500 B	3.5	7.5
27. G. M.	48.2	Carcinoma of pancreas	Partial pancreatectomy	4.45	14.0	4.24	15.0	630	550	2000 B	2.5	10.0
28. P. B.	48.0	Carcinoma of pancreas	Total pancreatectomy	4.78	12.0	3.18	8.5	660	107	2000 B	7	10.0
29. M. G.	67.0	Recurrent chordoma	Radical resection	4.75	14.5	2.32	7.5	0	650	2500 B	2.5	10.0
30. M. K.	52.0	Carcinoma of gall bladder	Radical resection	3.18	12.5	–	–	–	–	1500 B	2	10.0
31. M. K.	72.0	Carcinoma of pancreas	Partial pancreatomy	5.00	15.0	4.20	12.0	600	400	1000 B } 600 P }	2	9.0
32. I. B.	62.0	Carcinoma of cecum	Radical resection	3.20	8.5	3.80	10.0	870	1070	2000 B	2.5	10.0
33. N. A.	55.0	Carcinoma of stomach	Radical resection	4.10	9.7	4.27	12.0	30	760	2000 B	4	10.0
34. R. J.	52.0	Carcinoma of stomach	Radical resection	4.10	12.0	–	–	–	–	2000 B	3	10.0
35. G. R.	49.0	Carcinoma of stomach	Radical resection	3.70	10.0	5.15	13.0	400	425	1500 B } 600 P }	3	11.5
36. M. F.	70.0	Carcinoma of pancreas	Pancreatoduodenectomy	4.68	14.0	3.40	11.5	450	1320	1000 B } 850 P }	4	12.0
37. M. L.	69.0	Ruptured pregnant uterus	Delivery and hysterectomy	–	11.5	–	9.8	1000	1275	2500 B	3	12.5
38. C. C.	66.0	Carcinoma of stomach	Radical resection	4.26	13.0	5.02	14.5	130	235	2800 B	3.5	14.0
39. G. J.	61.0	Recurrent sarcoma of duodenum	Radical resection	4.60	13.0	3.60	11.0	600	960	2400 B } 300 P }	3.5	14.0
40. R. G.	61.0	Common duct stone	Cholecystectomy and choledochotomy	4.27	12.0	2.58	8.9	0	0	2500 B	4	15.0
41. H. H.	65.0	Carcinoma of pancreas	Total pancreatectomy	4.38	13.0	4.29	15.0	580	270	3200 B	4.5	17.5
42. W. F.	73.0	Recurrent carcinoma of stomach	Radical resection	4.40	14.0	3.80	11.5	0	1110	3500 B	3.5	17.5
43. B. Z.	54.0	Ulcerative colitis	Partial colectomy	5.08	12.0	3.64	11.0	1000	800	1000 B } 1500 P }	2	17.0
44. F. H.	60.0	Carcinoma of pancreas	Pancreatoduodenectomy	4.17	13.0	5.40	15.6	1215	2600	3600 B	4	20.0
45. J. H.	60.0	Gastric ulcer	Gastric resection	3.10	9.0	4.10	12.5	–	–	2700 B } 1000 P }	5	20.0
46. M. F.	62.0	Carcinoma of pancreas	Pancreatoduodenectomy	4.10	11.0	4.00	11.0	800	1000	3300 B	4	20.0
47. P. H.	60.0	Carcinoma of pancreas	Pancreatoduodenectomy	3.30	13.0	3.37	13.0	–	–	3500 B	3.5	22.0
48. S. B.	52.5	Carcinoma of pancreas	Pancreatoduodenectomy	3.52	10.5	3.60	11.5	250	950	2600 B	3	25.0
49. A. H.*	70.0	Carcinoma of stomach	Radical resection	3.91	13.7	–	–	–	–	3000 B } 1000 P }	3.5	25.5
50. G. L.†	117.8	Carcinoma of pancreas	Pancreatoduodenectomy	3.62	11.0	–	–	–	–	6000 B	6	30.0
51. H. D.	65.0	Carcinoma of pancreas	Pancreatoduodenectomy	4.30	13.5	4.20	12.0	900	2085	3500 B } 2600 P }	4.5	41.0
			Extremities									
52. H. B.	75.0	Sarcoma of ilium	Partial excision	3.96	13.6	3.83	12.2	800	2250	1800 B	3	7.5
53. R. L.	63.0	Crushing injury of leg	Débridement and cast	–	–	3.60	11.2	1775	2775	2000 B } 1500 }	4	22.0

*Died of shock six hours after ligation of portal vein.
†Died of shock two hours after ligation of portal vein.

tained approximately 4 Gm. of citrate for each 500 c.c. In Fig. 2 the patients have been classified according to the amount of citrate in grams which they received in given periods of time.

From unpublished work in this laboratory,[4] the lethal dose of sodium citrate in dogs was found to be approximately 0.30 Gm. per kilogram of body weight when given in fifteen minutes or less. When the time

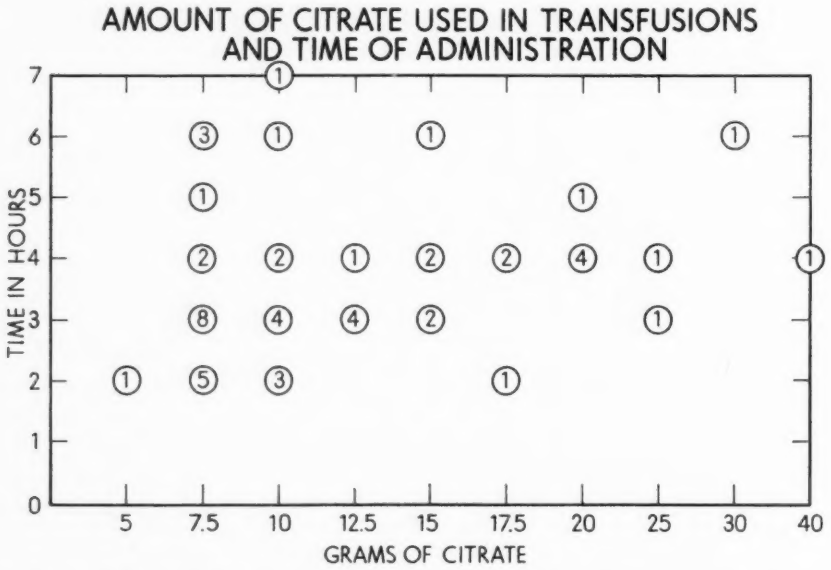

Fig. 2.—In this chart the patients have been classified according to the grams of citrate they received in given periods of time.

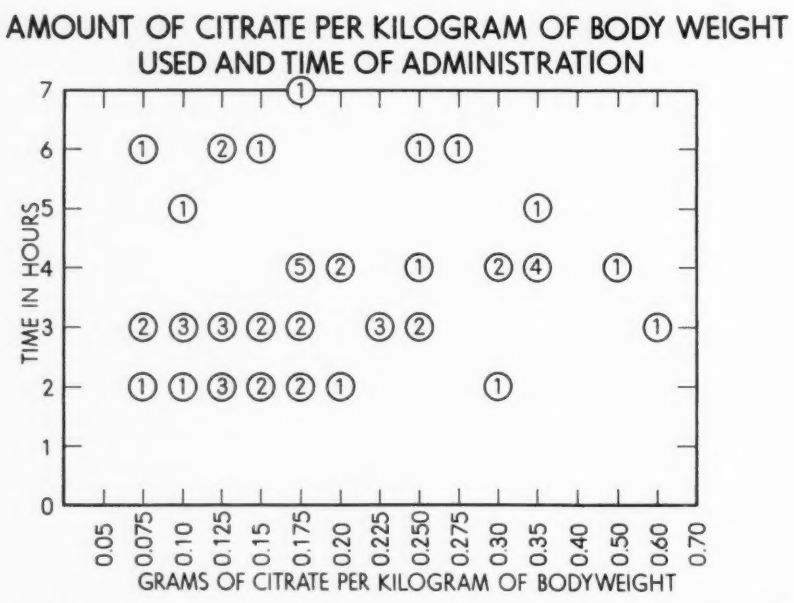

Fig. 3.—Chart showing the number of patients classified according to the grams of citrate per kilogram of body weight in various periods of time.

of administration is prolonged to two hours, as much as 1 Gm. of citrate per kilogram has been given with survival of the animal.[4] Most of our patients received from 0.10 to 0.30 Gm. of citrate per kilogram of body weight in from two to three hours as seen in Fig. 3. In spite of these large transfusions, our patients did not receive a per kilogram dose of citrate equal to the lethal dose in animals, since the time of administration was relatively slow.

DISCUSSION

The loss of blood at major surgical procedures generally exceeds that estimated at the time of operation. From 1,000 to 1,500 c.c. of blood are not infrequently lost even though care is given to hemostasis. White and Buxton[3] have shown that even larger volumes may be lost. Blood loss measurements were made in five of our cases. The amount lost in these patients was found to range from 2,100 to 3,100 c.c. of blood which is fairly representative of the group presented. Several years ago one of us (J.G.A.) measured the volume of blood lost in ten patients undergoing less formidable operations. Even here the loss of blood ranged from 175 to 695 c.c. The actual measurements of blood loss in our experience has nearly always exceeded our clinical estimate. For this reason we have tried to maintain a constant transfusion throughout the course of the operative procedure in the patients, at a rate sufficient to replace the estimated loss.

The good postoperative condition of these patients serves to emphasize the value of massive blood and/or plasma replacement. With the exception of the two patients who died on the operative day from surgical complications, none experienced postoperative shock. This experience is in marked contrast to that of several years ago when we practiced the less liberal transfusion of blood. Furthermore, none of the patients who received massive transfusions demonstrated any untoward reactions such as pulmonary edema or acute hemolysis resulting from mismatched blood. Of the patients who died before leaving the hospital, none could be considered as dying from the transfusion. It is to be noted that most of these patients maintained a satisfactory urinary output during the first two postoperative days. Furthermore, the red blood count and the hemoglobin after operation in most patients compared favorably with the preoperative studies. In twenty-one patients, however, the postoperative red blood count and hemoglobin determinations were diminished suggesting that these patients were undertransfused.

Considerable caution was exercised in the selection of suitable blood to be given to the patient. Every effort was made to give the patient blood of his own type. The universal donor (Landsteiner type O) was given only to patients of type O with one exception. Patients of types AB, A, and B were given blood of their own types. When blood

is rapidly administered in large volumes, it is not feasible to cross-match the patient's blood after each transfusion with each new donor blood before its administration. Instead, each donor blood of suitable type was cross-matched with the preoperative blood sample of the patient and then administered consecutively, the transfusion flask being rinsed with about 50 c.c. of saline solution before the next transfusion was added. No attempt was made to cross-match the bloods of the donor samples with each other.

One patient, however, did have a severe reaction. This patient's blood was Landsteiner type A and she was given five consecutive transfusions of type O blood. Nine hours later she was given a sixth transfusion, this one of type A. The patient developed icterus and oliguria. The nonprotein nitrogen rose to 85 mg. per cent by the second day but returned to normal at the end of a week. The patient's serum was Rh positive, thereby excluding the possibility of the Rh factor as a cause of the reaction. It is likely that the agglutinins *ab* in the donor blood reached an incompatible concentration with the patient's cells. It is also possible that the administration of type A blood after five type O bloods may have aggravated this condition. The reaction in this patient suggests that where multiple transfusions are concerned it is desirable to use donors of the same type as the patient.

Ivy and co-workers[1] postulated that if 1,500 to 2,500 c.c. of citrated whole blood or plasma were given rather rapidly to a 154-pound man after massive hemorrhage it may prove to be fatally toxic. This amount of blood or plasma would contain from 7.5 to 20.0 Gm. of sodium citrate as employed in our studies. Nine of our patients received 20 Gm. or more of citrate without incident, and of this group seven weighed less than 154 pounds as seen in Figs. 2 and 3. While nine of our patients did receive a per kilogram dose of citrate in excess of the lethal dose for dogs, the period of time in which they were transfused was considerably longer than that in which the lethal dose was experimentally determined.

Much of the recent concern over citrate intoxication associated with massive transfusions would seem to be unwarranted from the study of the patients presented here. The transfusion period in our cases ranged from two to six hours. This relatively prolonged period of transfusion time undoubtedly permitted considerable metabolism and excretion of citrate, thereby preventing the cumulative toxic effects of the drug.

The caution of Ivy and associates[1] about the use of large citrated transfusion from their work on dogs is based on experiments which do not simulate conditions clinically seen in man. In their experiments dogs were bled severely and an average of about 60 per cent of their individual blood volumes was replaced with citrated blood in a five-minute period. If a comparable amount of citrated blood or plasma were to be administered to a 154-pound man, about 4 liters would have to be administered in five minutes. This extremely rapid rate would hardly be applicable in either war casualties or civilian surgery. Much

of Ivy's work has been repeated in this laboratory, and when such rapid administration of citrated blood is undertaken, a very high mortality occurs in the experimental animal. If, however, the transfusion is given at a rate which is more nearly comparable to that employed in man, the dogs tolerated the transfusions well.

The toxic effects of citrate are thought to be attributable primarily to the immobilization of the calcium ion. In dogs we[4] have found that the lethal dose of citrate is greatly increased if ionizable calcium is given either intermittently or continuously throughout the course of a massive citrated blood transfusion. Although we have not observed any untoward effects associated with citrate transfusions in man, it is likely that if such did occur, the intravenous administration of ionizable calcium salts would exert a beneficial effect. This has been demonstrated in patients by Hill and Muirhead,[5] and others.

CONCLUSIONS

1. It is obvious from the data presented that the risk of citrate poisoning associated with the administration of large transfusions is negligible as currently practiced. Whatever the toxic properties of citrate may be, it is apparently detoxified rapidly enough so that it does not present a problem in the use of massive transfusions in man.

2. Not only did our patients tolerate their massive transfusions well, but we believe that without the liberal use of blood or plasma most of these radical operative procedures could not have been carried to a successful conclusion.

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BLOOD AND PLASMA TRANSFUSION SERVICE

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THE demand for whole blood and plasma for the treatment of patients in all divisions of medicine and particularly in surgery has increased markedly during the past ten years. This is largely a result of wider acquaintance on the part of physicians with the value of these substances in numerous clinical conditions. Their specificity in the treatment of shock and hemorrhage, while well established ten years earlier, has been popularized by extensive use in World War II. The supportive value of blood transfusion in the rehabilitation of patients with sepsis and anemia is also receiving more recognition. The role played by the components of blood in regulating water balance, in promoting wound healing, in maintaining nutrition, and in combating infection also adds to the demand.

As physicians return to civilian practice the provision by the average hospital of properly prepared whole blood and plasma in suitable form and in amounts required to meet the needs of practice will become a problem in every community. The technical aspects having been brought to at least a satisfactory stage of development by individual investigators, this becomes largely a problem in organization for community needs.

The first and most obvious solution is that of the individual hospital supplying its own blood and plasma. Unless the hospital is very large, there are a number of objections to this plan. The cost of equipment and of trained personnel, proper supervision, space requirements, and the difficulties in maintaining without waste an adequate inventory of blood of the various groups and of plasma reserves properly preserved are indeed tremendous obstacles in the way of effective and economical operation. Strumia believes that this statement is true only for hospitals with less than a 150 average daily census.[1] The operation of banks for whole blood is quite feasible in hospitals with a census of over 150, but, if whole blood reserves are depleted for plasma production, it has been our experience that reserves of whole blood of the various groups are difficult to maintain even in a hospital with an average daily census of 500 or over.

Assuming that the hospital is large enough to operate effectively a bank for whole blood, the plasma could then be purchased from a commercial house. There are three objections to this plan. First, the

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commercial house must pay professional donors and the cost to the patient rises accordingly. Second, since repayment to the commercial house must be made in money, indigent patients become a financial burden to the community and friends and relatives of patients of all economic classes are afforded no opportunity to make at least partial repayment in blood donations. The third objection is that the reserves in the whole blood bank within the hospital cannot be coordinated with plasma production.

One method of overcoming these obstacles in the way of economical and effective operation would be the establishment of well-organized community blood and plasma transfusion centers with a group of hospitals participating. When several hospitals unite in a cooperative effort, equipment and personnel can be fully utilized and the waste incident to duplication of many items in small organizations eliminated. When friends and relatives of the patients can serve as free blood donors, the cost of the product can be reduced to meet any income. The scope of the project appeals to those physicians interested in contributing to the knowledge in this field, and competent medical direction can be easily secured on a volunteer basis. While there are not University hospitals in every community needing such a center, universities might well lead the way, and the larger institutions in other communities would follow.

It is my purpose to describe briefly the blood transfusion service which has been developed in the department of surgery at the University of Cincinnati and the Cincinnati General Hospital from the standpoint of its relation to fifteen hospitals in the metropolitan area and to the community. There is no need for reference to the methods, techniques, and equipment used in the drawing of blood and in the preparation and processing of plasma. These are almost identical to those outlined by Strumia, McGraw, and Reichel.[2] Other details of operation have been described before.[3]

The service, with headquarters at the Cincinnati General Hospital, began operation Dec. 10, 1938, for the production of whole blood and plasma. Two years later equipment was added for the processing of plasma in the frozen and dry forms. The facilities include office space, forms suitable for accurate recording of transactions, rooms equipped for the drawing of blood from donors, a blood storage room with large refrigerator, and a laboratory for cleansing and assembling donor sets and for the testing of blood. Another laboratory room is equipped for the preparation of liquid, frozen, and dry plasma. This includes a set of torsion scales, a large centrifuge, a laboratory desk equipped with compressed air lines and suction apparatus for the pooling and redistribution of plasma, mechanical refrigeration equipment, a low temperature storage cabinet, an automatic shelling chamber, and a vacuum pump, condensor, and oven for drying plasma for the frozen state.

The service is directed by a member of the attending staff of the department of surgery and by a representative from the resident staff. A secretary, five laboratory technicians, a diener, and three student assistants are employed. Four trained part-time volunteers serve at regularly scheduled hours.

The products of the service are whole blood of all four groups, with Rh determinations if requested, plasma in the liquid, frozen, and dry states and red blood cells suspended in dextrose solutions. Whole blood is dispensed only at the request of a physician for a specified patient and on receipt of a simple form containing information necessary for recording the transaction. These forms are provided to the hospitals in advance and distributed at nurses' desks. It may be stated here that, in relation to hospitals other than the Cincinnati General Hospital, the service is not intended to replace the normally operating functions of the hospital pertaining to the transfusion of whole blood. Instead, it is planned to supplement these functions with a service which will make compatible and suitable blood quickly available whenever needed. In the majority of instances in any hospital the proper donor may be found among friends of the patient without undue delay. The service is of value where friends or relatives of the patient cannot be located or are not of the compatible blood group, or when an emergency exists which does not permit waiting for laboratory search.

Plasma is prepared in each of its physical states, liquid, frozen, and dry, because of the advantages and disadvantages peculiar to each form in relation to the service. A small inventory of twenty to thirty units (250 c.c. per unit) of liquid plasma, which is constantly being replaced with fresh units, is maintained because it does not have to be either thawed or restored with water for use. Liquid plasma is not stored as such for long periods because of the danger of bacterial growth, the rapid deterioration of prothrombin, complement, and fibrinogen, and the slower but progressive loss of albumin, globulin, and specific antibodies.

Most units of plasma are frozen immediately after distribution from the pools and held in a chamber at −40° C. In the frozen state opportunities for bacterial growth are minimized and there is little if any deterioration of components. These units are issued with instructions for thawing in a water bath at 37° C. The only disadvantage of these as compared with liquid units is the time, from twenty to thirty minutes, required for thawing. They are not issued to hospitals long in advance of need because of the low temperature refrigeration requirement.

A great portion of the plasma prepared by the service is dried from the frozen state. The advantages of dry plasma are that it can be transported and stored in the participating hospitals long in advance of need under all ordinary conditions of temperature, it can be restored for use with distilled water in from two to three minutes, and it can be used in the concentrated form if desired. The disadvantage

is that prothrombin and complement content is reduced. All hospitals participating in the service are given a supply of dry plasma for use in emergencies or any other cases in which its use is elected.

Red blood cell preparations, after centrifugation and removal of the plasma, are held in the refrigerator at 4° to 6° C. and are issued either as saline-glucose suspensions or as they are for suspension by the user as the occasion demands. They are discarded if not used after five days. In recent months most units of cell suspensions have been spoken for and are on reserve before the pool is completed.

When plasma or red cell suspensions are used, the information needed by the service for its records is entered on the same forms used for whole blood. For liquid or frozen plasma or red cells these forms are presented to service headquarters at the time the product is issued and for dry plasma they are forwarded by mail or messenger within a few days after the units are administered to the patients. On these forms are spaces for the amount of whole blood or plasma desired, the name of the patient, the method of repayment, if it has been decided upon, the signature of the physician, and the signature and address of the responsible relative or friend. Neither the physician nor the hospital assumes any responsibility for seeing that repayment is made. The physician is asked merely to explain the obligation to the patient or his relatives at the time the slip is signed, and the hospital merely to see that the service receives the forms properly filled out.

We believe that much of the success of this project is due to the fact that repayment of the obligation to the service is made according to the circumstances of the patient and his family. These circumstances are indicated on the request forms by the physician. Most patients fall into one of four classifications. If the patient has the money and has willing blood donors, the charge is $12.50 and one donor for each unit of blood (500 c.c.) or plasma (250 c.c.); if he has the money and has no willing donors the charge is $25.00; if he has willing donors but no money, two suitable donors are accepted for each unit used; if the patient is indigent and has no friends willing and able to serve as donors, the blood or plasma is supplied without obligation out of reserves obtained from the two-for-one trades. Red blood cell suspensions are a by-product of plasma preparation and are charged for at one-half these rates. All classifications are flexible and obligations are always adjusted to meet the circumstances. For example, if a patient who is neither indigent nor well-to-do has received eight or nine units of plasma and has been subjected to the expense of protracted hospital and medical care, any part of the accrued obligation either in blood donors or in money is acceptable as payment in full. A statement by the patient's doctor as to the limit of the ability to pay is accepted as final. In any event, no method of collection other than a simple statement of obligation is ever used. At no time during the five years of operation of this service has blood or plasma been refused, the re-

serves have never been exhausted, and no blood has been purchased from donors by the service. The financial experience resulting from this method of operation is recorded later in this communication.

Donors present themselves at central headquarters during three regularly scheduled half-day periods each week. At these times a physician is present to draw the blood. He is paid by the participating hospitals, the share of each being prorated according to the number of transactions during the preceding month. This amounts to about 40 cents for each transaction. There is no other charge made to hospitals by the service.

In a few respects the operation of the service for patients in the Cincinnati General Hospital differs from that for patients in other hospitals. Since all patients in the General Hospital are on a free medical service basis, all repayment is made with blood donors. No cash transaction is ever involved. Also, donors are received at any time of the day or night, since the blood is drawn by the intern or house doctor concerned and the appointment made through him. A technician and other facilities of the service are at his disposal at all hours. Within the General Hospital, replacement of a unit, blood, or plasma becomes the obligation of the hospital service, such as medicine or general surgery, to which it was issued. Each hospital service is held responsible for a balance of its own debit and credit columns in the monthly record of transactions compiled at service headquarters. In this way an obligation is not canceled when a physician who makes a withdrawal is transferred to another service or terminates his residency. Since the obligation is met by the service, replacement is on a unit-for-unit basis within the General Hospital. In turn, the General Hospital provides rent-free space, heat, light, laundry, and chemicals used in donor booth and in laboratory operation.

The usefulness of this service to the community is indicated by its degree of growth expressed in terms of the number of transactions of units of whole blood and plasma. In the four years of operation there has been a progressive increase from 2,687 units for the first twelve months of operation to 4,410 units for the year 1942, and to 5,780 units for the year 1943.* This is an increase of 115 per cent and it has occurred without any attempt at promotion. Continued recent growth is shown by a comparison of the experience in transactions for the six-month period from January, 1943, through June, 1943, with the six-month period from July, 1943, through December, 1943. During the first period there were 2,780 transactions as compared with 3,000 during the second period. It is worth noting here that during these same six-month periods the use of whole blood dropped from a figure of 2,111 to 1,929 while the use of plasma increased from a figure of 669 to 1,071 units.

*These figures represent units of whole blood (500 c.c.) and plasma (250 c.c.). They do not include units of red blood cell suspensions.

The financial experience of the service has been satisfactory, particularly since it was not intended to operate to a profit. The expenditures include salaries for secretarial and technical personnel, supplies for the office and laboratory, and maintenance on refrigeration and laboratory equipment. Medical direction is volunteered. The cost of items furnished by the Cincinnati General Hospital is difficult to estimate and is not included. This omission tends to make the following figures misleading, but it must be remembered that in return this hospital receives all its transfusions on a unit-for-unit basis with no cash transactions. The income to the service is derived entirely from patients who are paying for private hospital and medical care and who have received blood or plasma from the service. The total expenditures for the year 1943 were $10,250. The cash receipts for this period were $12,739. The difference of $2,489 is adequate to meet the cost of depreciation in fixed equipment. Since during this same period there were 5,780 transactions in blood and plasma, each transaction cost the service less than $2. This cost was paid by the patients who received the benefits, at the rate of not more than $25 or $12.50 and one donor for each unit. In no instance has there been more than a simple statement of obligation to the patient in attempt at collection, and blood and plasma in any amount requested have always been issued regardless of the financial circumstances of the patient.

The operation of the service described has been successful in Cincinnati, but it is not to be expected that it will suit exactly all communities. Variations in the plan can easily be made in order to adapt it to particular needs. The number and sizes of the participating hospitals and the distances between them are the variables. For example, hospitals at long distances might make periodic collections of blood from friends and relatives of patients and transport them to the center in trade for frozen and dry plasma. Hospitals close to the center might prefer to have the blood collected there and to draw out both whole blood and plasma. By the adoption of standard apparatus for the collection of blood and standard techniques on the part of all participating hospitals, the plan could be as flexible as necessary to meet the particular requirements of each community.

Because of the demands on medical personnel and the necessary restrictions on material, organization of blood and plasma services, as far as civilian medical practice is concerned, can proceed very little for the duration of the war. After the war adequate medical care must include blood and plasma services that meet the requirements of the patient, the physician, and the hospital. A community service similar to that just described is one solution to the problem. The patient receives blood and plasma in the amount needed regardless of his financial circumstances. If payment in money cannot be made he still may participate by supplying blood donors from his friends and relatives. There are no restrictions placed on the physician either by the

amounts of blood or plasma readily available or by the financial ability of his patient. The participating hospital, too, receives the advantages of being able to furnish blood and plasma in all cases, without the necessity either of an independent service, with attendant problems in supervision or expense, or of purchase of a commercial product for charity patients. Finally, this service is one which is supported within the community and which is paid for by those who receive the benefits, without excessive cost to the individual and without governmental subsidy.

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GELATIN AS A PLASMA SUBSTITUTE

A Preliminary Report of Clinical Experience

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NEED for a plasma substitute which would be readily available, innocuous, stable, therapeutically effective, and easily reproducible in respect to its physical and chemical properties led to renewed interest in gelatin as an intravenous solution to supplement the supply of plasma.

In 1915, Hogan[1] reported that gelatin-saline solutions would restore falling blood pressure when administered to patients in shock. With the war-induced stimulation of investigations of plasma substitutes there have appeared a number of reports on the efficacy of gelatin as a plasma substitute.[2-8] Previous studies in this department led us to believe that the specially prepared ossein gelatin with which we were supplied was an effective agent in the treatment of hemorrhagic shock in dogs. The absence of toxic reactions in dogs and rabbits following massive infusions with gelatin encouraged us to proceed to administer gelatin intravenously to human subjects without fear of pyrogenic and antigenic reactions or of producing liver or kidney damage.[9]

In the interest of carrying out a broad evaluation of gelatin as a plasma substitute our plan of study has included the following phases:

1. The evaluation of gelatin as a means of treating shock from trauma, hemorrhage and burns.[10]
2. A study of the possible toxic manifestations of gelatin on liver and kidney functions including the pyrogenicity and antigenicity of gelatin.[9, 10, 11]
3. The effect of gelatin on the circulating serum proteins.[9]
4. The disappearance of gelatin from the blood, its excretion, and possible utilization.[9, 10]
5. The significance of the phenomenon of pseudoagglutination of red cells in relation to sedimentation rate and clotting time.[10]

The Chas. B. Knox Gelatine Company, Johnstown, N. Y., supplied the gelatin solutions through the courtesy of Dr. D. Tourtellotte, and provided the University of Pennsylvania with a grant to defray a part of the cost of the study.

Preliminary reports of this work were presented at a conference on gelatin convened by the Subcommittee on Blood Substitutes of the National Research Council, Washington, D. C., Sept. 24, 1943, and at the meeting of the Physiological Society of Philadelphia, Jan. 18, 1944.

Presented at the meeting of the Society of University Surgeons, Nashville, Tenn., Feb. 10-12, 1944.

6. A study of the histologic appearance of animal tissues after intravenous infusions of gelatin.[9, 12]
7. Investigation of the influence on protein metabolism of gelatin solutions fortified with those amino acids in which it is known to be deficient.
8. The effect of intravenous gelatin on oxygen transport.
9. The clinical response of patients to intravenous gelatin infusions.
10. The effectiveness of gelatin solutions in the treatment of edematous states associated with hypoproteinemia.
11. An evaluation of the effect of gelatin on the cardiac output as measured by the ballistocardiograph.
12. The effect of gelatin infusions on blood volume and plasma osmotic pressure.
13. Comparison of the clinical effectiveness of gelatin solutions subjected to varying degrees of molecular degradation by prolonged autoclaving.

Our observations on the first six of these have been or are being published,[9-12] and most of the others are under study at the present time.

This report deals briefly with our clinical experience with the first 100 patients in our series to receive gelatin. In a general way it suggests the probable future place of gelatin in therapeutics and explains the trend which our studies have followed. Some of the previously reported studies in the dog have been repeated in man and we have included observations on the effect of gelatin infusions on serum protein concentrations as well as on functions of liver and kidney.

The clinical response of patients to intravenous gelatin is reported in some detail and a summary is given of our present tentative conclusions.

MATERIAL AND METHODS

Of the several types of gelatin available to us, we have perferred to employ that produced by hydrolysis of alkali-treated long-bone collagen under controlled and standardized conditions not attained in the usual manufacture of edible gelatin. We used both 6 per cent and 4 per cent solutions in 0.85 per cent saline. Most of the material was autoclaved at fifteen pounds pressure for twenty minutes although some of the material was autoclaved for 180 minutes to produce a small molecular size, a lower gel strength, viscosity, and modulus of rigidity. All of the specific quantitative studies here reported were obtained with the use of material autoclaved for 20 minutes.

The patients were chosen from the various wards of the Hospital of the University of Pennsylvania, those with poor prognoses being used first until we had repeated the tests for toxicity. Later, patients with specific clinical problems were used for an evaluation of gelatin as a

method of treatment. Another small group consisted of volunteer medical students, nurses, and blood donors, who formed the basis for data on normal subjects. One hundred thirty-two liters have been administered to 100 patients in 190 infusions.

The gelatin solutions were given with the usual hospital intravenous trays and have been found to be miscible with all the usual intravenous fluids. The only precaution which must be observed is in preventing the burette from cooling below normal room temperature, which will lead to the formation of a gel.

Blood analyses for proteins were carried out as follows:

1. Plasma proteins: Plasma was precipitated with trichloracetic acid and the precipitate analyzed for nitrogen.
2. Albumin: Plasma was precipitated with sodium sulfite according to the method of Campbell and Hanna[13] and the filtrate analyzed for nitrogen.
3. Fibrin: Plasma was precipitated with calcium chloride according to the method of Foster and Whipple,[14] and the precipitate analyzed for nitrogen.
4. Gelatin: Plasma was precipitated with sodium tungstate and sulfuric acid and the precipitate analyzed for nitrogen. The difference between No. 4 and No. 1 was taken as gelatin nitrogen.

All nitrogen analyses were done by Kjeldahl semimicro technique using the boric acid titration. We have been able to recover gelatin added to normal plasma with an error of ±5 per cent.

Hematocrit determinations were made on citrated blood in Wintrobe tubes, centrifuged at 2,500 r.p.m. for thirty minutes. Bromsulphalein retention was measured by the method of Rosenthal and White,[15] as modified by Helm and Machella.[16] Urea was determined by the method of Ormsby,[17] and urea clearance calculated from the formula given by Van Slyke.[18]

CLINICAL OBSERVATIONS

Clinical Records.—Records were kept in connection with all of the 190 infusions in 100 patients reported here. These included observations on temperature, pulse, respiration, and blood pressure taken at intervals during and after infusions as well as notes on any untoward subjective or objective reactions to the intravenous infusion of gelatin. Reactions of some type occurred as a result of sixteen, or 8.4 per cent, of the infusions as recorded in Table I. Two of these were serious reactions and fourteen were trivial. Only one can be definitely attributed to gelatin per se.

Cardiac decompensation occurred in a 58-year-old woman with known rheumatic cardiac disease and subacute bacterial endocarditis who appeared to be adequately compensated before the infusion. The infusion was stopped because of shortness of breath after 650 c.c. of 6 per cent

TABLE I

REACTIONS OBSERVED IN 190 INTRAVENOUS INFUSIONS OF GELATIN

TYPE OF REACTION	INFUSIONS	PER CENT
Serious Reactions		
Cardiac decompensation	1	0.55
Anaphylactoid reaction (Nonspecific)	1	0.55
Total	2	
Minor Reactions		
Dizziness or headache	4	2.1
Nausea or vomiting	1	0.55
Precordial distress	2	1.1
Systolic blood pressure rise	2	1.1
Phlebothrombosis	5	2.6
Total	14	

gelatin had been given over a period of fifty minutes. Twelve hours later there was a moderate rise in pulse rate and respiratory rate and fourteen hours later acute pulmonary edema developed. The patient responded temporarily to the usual treatment but died five days later. This unfortunate occurrence cannot be attributed to any toxic properties of gelatin but serves to illustrate the dangers inherent in the intravenous administration of a hyperosmotic macromolecular colloid to individuals with impaired cardiac reserve.

The other serious reaction occurred in a 56-year-old white man with a gastric fistula and biliary tract fistula which resulted from abdominal echinococcus disease. Within five minutes after commencement of the first infusion of gelatin he began to itch and become apprehensive. His pulse rose markedly and blood pressure dropped to 40/20 from his normal of 90/70. There was no chill or temperature rise. Within twenty minutes after the administration of 0.5 c.c. of epinephrine, his conditions. Because of the frequency of such reactions in this patient, detailed reactions to intravenous blood, plasma, normal saline solution, 5 per cent glucose in water, 2 per cent saline solution, and amino acid solutions. Because of the frequency of such reactions in this patient, detailed records of his blood pressure and pulse during these episodes were not kept. Subsequent intracutaneous and subcutaneous test doses of all the ingredients of the gelatin solution as well as the solution itself and similar preparations yielded no evidence of sensitivity.

Dizziness and headache occurred following four infusions of 100 c.c. of 6 per cent gelatin in ambulatory subjects. This reaction was not noted among subjects who were resting in bed. One highly nervous woman patient with biliary tract disease became nauseated and vomited immediately after an infusion of 580 c.c. of 6 per cent gelatin in forty minutes. The reaction was apparently related to the ingestion of ice cream immediately before the start of the infusion. Precordial distress of a mild and temporary character was noted by two normal male subjects in the course of infusions of 6 per cent gelatin of 750 c.c. in ninety-five minutes and 1,000 c.c. in seventy minutes.

Elevations in systolic blood pressure of 30 to 40 mm. of mercury were noted in two individuals of normal circulatory status who received 580 c.c. of 6 per cent gelatin in forty minutes and 625 c.c. in thirty minutes, respectively. Both infusions were discontinued at this point. One subject had received four previous infusions of 1,000 c.c. each without untoward effects. In both cases the blood pressure returned to normal within three to four hours. Rises of systolic blood pressure greater than 10 to 15 mm. of mercury were not noted in other subjects with the exception of those with pre-existing hypotension.

Thrombosis at the site of injection occurred following five infusions. In four of these cases the needle remained in the vein for many hours in the course of circulatory studies or the continuous administration of intravenous fluids. In our experience this is considerably less than the incidence of thrombosis following blood or plasma infusion. A review of fifty of the most recent infusions in thirty-three patients with an examination of veins for evidence of thrombosis revealed five of the forty-seven veins infused to show some evidence of thrombosis. In these same patients there were eight veins that had not been used for gelatin infusion which showed signs of obvious thrombosis.

Febrile reactions were noted following infusions of gelatin in three patients. Two of these patients had widespread malignant lesions and an irregular febrile course before infusion. Both of these patients had received previous gelatin infusions without reaction and one received several subsequent uneventful infusions. The third patient, one employed in studying the effect of gelatin on cerebrospinal fluid pressure, exhibited fever, headache, meningismus, and pleocytosis of the cerebrospinal fluid following the administration of gelatin. In this case a malleable spinal needle attached to a manometer remained in the subarachnoid space for three and one-half hours and the mechanical irritation apparently accounted for the meningeal reaction.

The postoperative administration of gelatin to patients subjected to major surgical procedures was attended by beneficial effects which were unmistakable to all observers. All of these patients exhibited the improvement we have come to associate with repeated small plasma transfusions. In several patients found to have inoperable tumors at laparotomy, the use of repeated gelatin infusions seemed to delay the expected downhill course and enabled us to carry them along for the usual postoperative period, transferring them for further care in far better condition than we have been accustomed to expect.

Two patients with large obstructing gastric carcinomas were kept in apparently excellent condition with intravenous glucose and daily gelatin infusions for periods of nine and ten days respectively. A number of patients commented spontaneously upon their subjective improvement following gelatin.

Although clinical impressions concerning the beneficial effect of gelatin infusions cannot be scientifically measured, and are not by themselves

an adequate basis for conclusions, the apparent subjective and objective benefits resulting from gelatin administration to these patients have been important factors in encouraging us to continue the work.

Infusions Repeated After a 14-Day Interval.—Nine subjects received repeated intravenous infusions of gelatin after the lapse of the fourteen-day interval commonly accepted as the critical period for the development of anaphylactic hypersensitivity. None of these individuals gave any subjective or objective evidence of this type of reaction.

Erythrocyte Sedimentation Rate.—A marked increase in the erythrocyte sedimentation rate after gelatin infusions in dogs was previously reported.[10] That this phenomenon also occurred in man was obvious to all who worked with the human blood samples. This impression was confirmed by determination of the corrected sedimentation rate in two normal subjects before and after infusions of 1,000 c.c. of 6 per cent gelatin. The sedimentation of erythrocytes was markedly accelerated in both instances. The probable relationship of this phenomenon to pseudoagglutination of the red blood cells was discussed in the report previously cited.

Blood Coagulation Studies.—Determinations of the clotting time of whole blood were made on seven subjects before and three hours after the infusion of 6 per cent gelatin solution in amounts varying from 500 c.c. to 1,000 c.c. The results are shown in Table II.

TABLE II

EFFECT OF INTRAVENOUS GELATIN (6 PER CENT) ON THE CLOTTING TIME

PATIENT	VOLUME C.C.	CLOTTING TIME	
		BEFORE	3 HR. AFTER
B.J.	1,000	15	15
R.S.	1,000	13	9
J.L.	1,000	19	22
M.S.	500	19	27
M.F.	500	16	17
S.D.	1,000	14	6
S.L.	1,000	13	8
	Average	16	15

The average clotting time before infusion was sixteen minutes and after infusion was fifteen minutes. In only one case (M. S.) was the clotting time appreciably prolonged following infusion. Since the method gives rather variable results, little significance can be attached to this isolated observation. This is in contradiction to the animal work previously reported in which the clotting time after gelatin infusion was found to be uniformly prolonged in dogs.

Twenty-four patients were given infusions of gelatin before, during, and shortly after major surgical procedures. None of these showed any clinical evidence of impaired coagulability of the blood or of delay in wound healing.

Bromsulphalein Liver Function Test.—In the dog, the only abnormal finding in the liver function studies was the progressive retention of bromsulphalein with each of a series of repeated infusions of gelatin. Similar, although less marked, results were seen after plasma infusions, and chiefly for this reason the phenomenon was assumed not to represent a specific impairment of liver function due to gelatin.

No bromsulphalein retention was seen after single or repeated infusions of gelatin in seventeen patients although in control studies with blood and plasma transfusions on human subjects the findings in dogs were substantiated. Further study of the influence on liver function of temporarily increasing the amount of circulating colloids will be necessary if these phenomena are to be explained.

Urea Clearance.—Urea clearance was determined before and after single and repeated infusions of gelatin in nine subjects.

The results obtained in the study of urea clearance before and after seven single infusions in five subjects are shown in Table III. The first two of these showed a moderate fall in urea clearance during the twenty-four-hour period following infusion, but the values were back to the preinfusion figures when urea clearance was determined two weeks later. The third patient also showed some immediate depression of clearance but no later observation was obtained. Two individuals showed no significant change in urea clearance after infusion.

TABLE III

UREA CLEARANCE AFTER SINGLE INFUSION OF GELATIN (6 PER CENT)

PATIENT	VOLUME (C.C.)	TIME (MIN.)	UREA CLEARANCE (%)	
			BEFORE	AFTER
A. F. (1)	1,000	60	113	87
				107*
J. H. (1)	1,000	70	116	89
				103*
G. A.	1,000	165	107	53
J. W.	1,000	120	114	107
L. N.	540	90	72	81
A. F.	790	96	90	120
			133	98
			144	96
				118
	Average		112	108
J. H.	750	90	122	113
			119	109
			101	135
			144	90
	Average		121	112

*Two weeks after infusion.

In an effort to evaluate these data more exactly, the infusions were repeated on the first two subjects after an interval of four weeks. Urea clearance was determined daily for three and four days respectively before infusion and for four days after infusion. The volumes

of 6 per cent gelatin given were somewhat smaller and were given more slowly than on the previous occasion. The average values for clearance before and after infusion show no significant change, nor was there any depression immediately after infusion. All of the values for urea clearance after gelatin infusion, regardless of the variation from previous values, indicate good renal function.

Urea clearance values determined in the study of repeated infusion of gelatin in five patients are shown in Table IV. The first two patients show a more pronounced fall in clearance than was observed after single infusion, but the values had returned to the patients' usual figures within three days after infusion. The last two patients had pre-existing impairment of renal function. One showed essentially no change after a series of five daily infusions. The patient, H. E., received a large quantity of gelatin in a little over forty-eight hours and there was a temporary depression of urea clearance followed by a return of function considerably above that observed initially (Fig. 1).

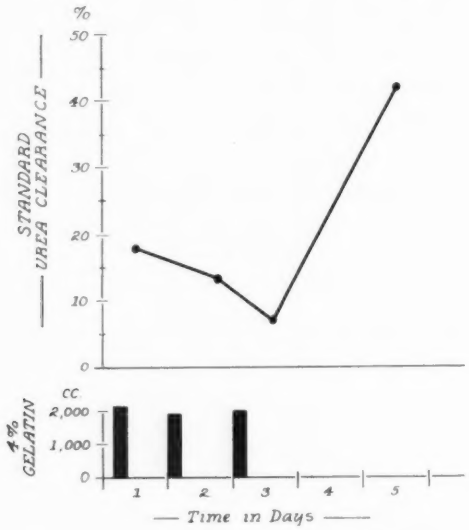

Fig. 1.—Urea clearance in the damaged kidney following gelatin infusion.

There is no evidence of any permanent change in renal function as determined by urea clearance after gelatin infusion even after the administration of large amounts to patients with pre-existing renal damage. Large quantities of gelatin given rapidly or in the form of repeated infusions, however, apparently cause a temporary impediment to urea clearance.

Serum Proteins.—Protein studies were done on thirty-nine patients, including seven normal subjects, four blood donors who were given gelatin after bleeding, eighteen carcinoma and brain tumor patients (including generalized carcinomatosis, carcinoma of gall bladder,

TABLE IV

UREA CLEARANCE AFTER MULTIPLE INFUSIONS OF GELATIN

PATIENT	NO. OF INFUSIONS	QUANTITY IN EACH INFUSION		BEFORE	AFTER INFUSION (NO. 1)	AFTER INFUSION (NO. 2)	AFTER INFUSION (NO. 3)	DAYS AFTER			
		VOLUME (C.C.)	PER CENT					2	3	4	5
N. T.	3	480	6	89	70	92	39	27	89		
J. G.	2	1,000	4	135	55	13		103			
L. N.	4	1,500	6	81				72		107	
J. M.	5	300	6	68							
H. E.	2	2,000	4	17	12	8			44		

hepatoma, Ewing's sarcoma, melanoma, carcinoma of lung, and lymphosarcoma). There were four patients with nephrosis, two with cirrhosis, one with epilepsy, one with a subdural hematoma, one with a bleeding peptic ulcer, and one with subacute bacterial endocarditis. The plasma proteins, albumin, globulin, fibrin, and gelatin were determined.

In most instances there was a drop in the serum protein concentration which could not be accounted for by the hemodilution as measured by hematocrit. This decrease involved the albumin, globulin, and fibrin fractions. The decrease in fibrin was the most constant and most marked finding, falling to zero in one instance. Total protein (plasma protein plus gelatin) was increased somewhat in the majority of patients.

No differences in behavior of the proteins were observed in the patients with carcinoma or cirrhosis, as compared with observations in the normal individuals (Table V). Even in those individuals whose plasma protein concentration was already very low, there was a further depression after gelatin infusion. Table VI shows the results of protein analyses on a patient with nephrosis whose initial serum protein was 3.93 per cent. In this patient after two gelatin infusions no fibrin was found by the Foster and Whipple[14] method, but ten days later

TABLE V

SERUM PROTEINS AFTER GELATIN (6 PER CENT) INFUSION

DIAGNOSIS	VOLUME (C.C.)	TIME	HEMATOCRIT (%)	SERUM PROTEIN (%)	GELATIN (%)	FIBRIN (%)
Normal	1,000	Before	40.3	6.45	0	
		3 hr. after	35.0	5.27	1.21	
				(5.73)		
Experimental hemorrhage 1,100 c.c.	840	Before	39.5	5.92	0	
		30 min. after	28.5	4.23	1.19	
				(4.99)		
Portal cirrhosis	1,000	Before	37.0	5.80	0	0.213
		3 hr. after	30.0	4.19	1.13	0.163
				(4.65)	(1.25)	(0.131)
Carcinomatosis			25.0	6.73	0	0.562
		Before	21.5	5.39	1.09	0.450
	1,000	3 hr. after		(5.64)	(1.14)	(0.476)

Figures in parentheses are corrected for change in hematocrit.

TABLE VI

SERUM PROTEINS ON A PATIENT WITH NEPHROSIS AFTER GELATIN (6 PER CENT) INFUSION

TIME	DAY	HEMATOCRIT	SERUM PROTEIN	ALBUMIN	GLOBULIN	FIBRIN	GELATIN
Before gelatin	1	26.5	3.93	2.37	1.36	.538	0
3 hr. after first infusion 1,000 c.c. 6 per cent gelatin	1	24.3	3.06 (3.15)	1.35	1.71	.413 (.425)	1.00 (1.03)
24 hr. after first infusion	2	22.5	3.39 (3.57)	1.79	1.60	.506 (.534)	.85 (.89)
3 hr. after second infusion 1,000 c.c. 6 per cent gelatin	3	24.0	3.03	1.62	1.41	.409	1.63
24 hr. after second infusion	4	23.3	2.94	1.73	1.31	0	1.26
10 days after second infusion	14	28.0	4.24	2.23	2.01	0	0.22
19 days after second infusion	23	26.0	4.18	2.07	2.11	.588	0

Figures in parentheses are corrected for change in hematocrit.

fibrin was back to a normal level. His clotting time remained normal. In a boy with nephrosis whose plasma protein was 2.83 per cent before a series of gelatin infusions, the plasma protein fell steadily after each daily infusion, reaching a level of 0.88 per cent with an albumin of 0.1 per cent. This fall in serum protein is a reversible change and after infusion of gelatin is stopped, the serum protein returns to its previous level as the gelatin disappears from the blood stream.

This depression of the serum proteins is seen with other types of gelatin and with other substances suggested as plasma substitutes. Following the use of hyperosmotic colloids such as gum acacia, which is not excreted in the relatively short time that it takes for gelatin to disappear from the blood stream, the depression of the serum protein concentration is remarkably prolonged.

With the ossein gelatin we have used, there exists a reciprocal relationship between the concentration of the serum proteins and the circulating gelatin. The gelatin disappears from the blood stream in three to five days, depending upon its degree of molecular degradation.

We are unable to explain the reduction in protein values, unless the presence of hyperosmotic gelatin in the circulating blood results in a temporary redistribution of protein between blood and tissue protein stores.

Venous Pressure.—Observations on the changes in the peripheral venous pressure were made at intervals during the course of twenty-one infusions of 6 per cent gelatin in fifteen subjects of relatively normal

cardiovascular status. In seven instances readings were also taken at intervals of one to twenty-four hours after the completion of the infusion. Venous pressure changes were also recorded as a part of the circulatory studies on six volunteers during acute experimental hemorrhage with gelatin replacement.

A rise in venous pressure, reaching a maximum at the end of the infusion, was consistently observed in all of the twenty-one experiments on normal individuals (Table VII). The changes varied from 10 to 90 mm. of water, the average increment being 52 mm. These scattered observations made at intervals after the completion of the infusion in a small group of cases indicate that the venous pressure is maintained at a high level, or may even reach a maximum, three to four hours after infusion but tends to return to normal levels within twenty-four hours.

All venous pressure measurements were taken in the same arm, and often in the same vein, as that used for the infusion of gelatin. It is, therefore, possible that the data may be subject to error as a result of venous spasm or increased viscosity of the blood due to the gelatin infusion. This view is supported by the data of Table VII, which shows no direct relationship between the venous pressure rise and the volume or the rate of infusion. One would expect to find such a relationship if the venous pressure changes are ascribed to increased blood volume.

TABLE VII

EFFECT OF GELATIN (6 PER CENT) ON VENOUS PRESSURE

PATIENT	VOLUME (C.C.)	BODY WEIGHT (KG.)	TIME OF INFUSION (MIN.)	RATE (C.C. PER KG. PER MIN.)	ELEVATION OF VENOUS PRESSURE ABOVE INITIAL LEVEL (MM. OF H_2O)		
					END OF INFUSION	3 TO 4 HR. LATER	24 HR. LATER
R. R.	1,000	45	100	.222	52	33	
A. F. (1)	1,000	77	60	.216	49		
A. F. (2)	790	77	90	.113	72	85	20
J. H. (1)	1,000	75	70	.190	50	46	14
J. H. (2)	750	75	90	.111	54		
J. W.	1,000	84	120	.099	25	38	4
M. Z.	1,000	70	60	.238	40	30	
J. S.	1,000	56	90	.198	29	67 (1 hr.)	
J. L.	1,000	71	75	.186	72		
S. D. (1)	1,000	77	140	.092	82		
S. D. (2)	1,000	77	90	.144	48		
S. L.	1,000	52	170	.113	72		
C. W.	1,000	75	75	.117	42		
A. S. (1)	1,000	49	120	.170	80		
A. S. (2)	1,000	49	115	.177	72		
C. K.	500	40	65	.192	62		
A. M.	500	83	100	.060	90*		
C. D.	500	46	35	.310	10		
J. M. (1)	300	49	90	.068	30		
J. M. (2)	300	49	90	.068	38		
J. M. (3)	300	49	90	.068	32		

*Unreliable—patient restless and uncooperative.

On the other hand, there appears to be a fairly consistent correlation between the increase in venous pressure and hemodilution, presumably accompanied by an increase in blood volume, as measured by the fall in hematocrit. Hemodilution is also maximal at three to four hours after infusion and returns toward normal in twenty-four to forty-eight hours (Fig. 2). This would suggest that the sustained rise in venous pressure is the result of an increase in blood volume due to the high colloid osmotic pressure of gelatin. The quantitative rise in venous pressure may be a factor of the hydration, blood volume, and circulatory status of the individual at the time of the infusion, rather than of the rate or volume of infusion. In this connection it is of interest

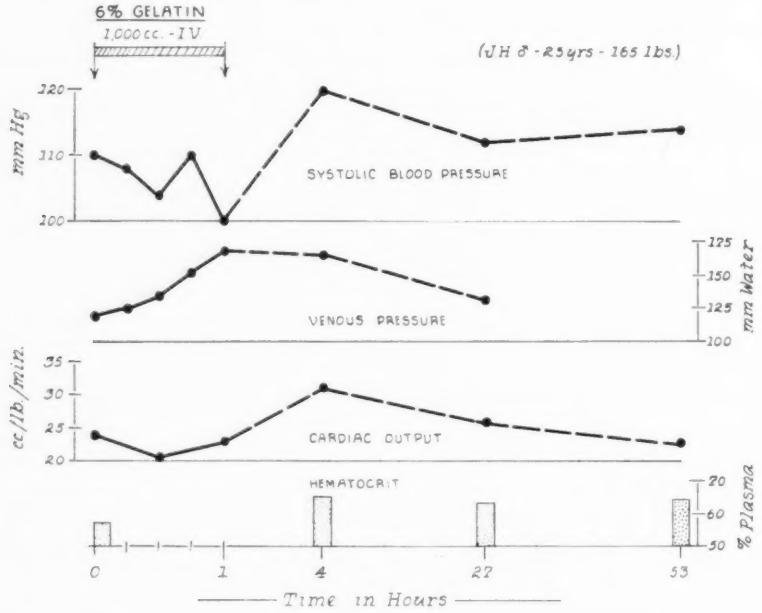

Fig. 2.—Effect of intravenous gelatin on cardiac output.

to note that the rise in venous pressure observed with gelatin infusion after experimental hemorrhage was less marked than that observed in normal subjects. Even with rapid infusions of 600 to 700 c.c. of 6 per cent gelatin in fifteen minutes the venous pressure was simply restored to its initial level and not excessively elevated.

Cardiac Output.—The cardiac output of nine subjects without demonstrable cardiovascular disease was studied before, during, and after a total of twelve intravenous infusions of 6 per cent gelatin solution.*

*These studies as well as those on acute experimental hemorrhage with gelatin replacement were done with the collaboration of Dr. James Hardy and carried out in the Department of Research Therapeutics. They will be the subject of a future publication.

The determinations were made by means of the ballistocardiograph, using the formulas of Starr[19] and reading the cardiac output in cubic centimeters per minute per pound of body weight. Ballistocardiographic records were also made in connection with the studies on acute hemorrhage with gelatin replacement in nine normal subjects.

Cardiac output was consistently increased after infusions of 750 to 1,000 c.c. of 6 per cent gelatin. The increase reached a maximum three to four hours after the completion of the infusion and returned to normal within twenty-four hours after infusion.

The changes in cardiac output can be correlated in general with the changes in hematocrit and venous pressure as illustrated in Fig. 2. This would suggest that the increased cardiac output may be due to increased plasma volume. The continued increase in cardiac output after the completion of the infusion would then represent a continued increase in plasma volume due to the movement of extravascular fluid into the circulating blood resulting from the strong osmotic effect of the gelatin colloid. This problem is now in process of further study by means of direct plasma volume determinations.

Acute Experimental Hemorrhage With Gelatin Replacement.—In order to study the effectiveness of gelatin as a plasma substitute in man under controlled experimental conditions, bleeding followed by replacement with intravenous gelatin solution was performed on nine healthy male volunteer blood donors. Observations were made on clinical signs and symptoms, blood pressure, pulse, venous pressure, hematocrit, and cardiac output. The latter was measured by means of the ballistocardiograph, using the formulas of Starr.[19] Subjects were bled 15 c.c. per kilogram of body weight (about 1,000 c.c. in most cases), followed by rapid replacement with two-thirds of that volume of 6 per cent gelatin solution (10 c.c. per kilogram). Observations were continued for about one hour following the infusion of gelatin.

In most cases bleeding of 15 c.c. per kilogram had a rather marked effect on the circulation. Many subjects exhibited signs of sweating, pallor, weakness, and dizziness. Usually there was a definite fall in blood pressure, venous pressure, and cardiac output. The pulse rate was quite consistently slowed with a compensatory increase in stroke volume. These changes are similar to those reported by Shenkin, Cheney, Govons, and Starr[20] following hemorrhages of similar magnitude. All of these values were rapidly restored to normal by replacement of two-thirds of the volume of blood removed with 6 per cent gelatin solution. The restoration of the circulation was accompanied by marked hemodilution, as indicated by the sharp fall in hematocrit values after the infusion of gelatin. Subjects experienced rapid relief of symptoms following gelatin replacement and were able to stand and walk without dizziness or discomfort.

Fig. 3 illustrates the data obtained on one subject who had an unusually severe circulatory collapse following hemorrhage.

Gelatin in the Treatment of Shock.—Four patients in shock were treated with gelatin. The first of these was a 35-year-old woman who was admitted in a critical condition with a blood pressure of 52/40 and a pulse rate of 144. She was cold, perspiring, and pale. Her history was suggestive of peptic ulcer and the diagnosis of a bleeding

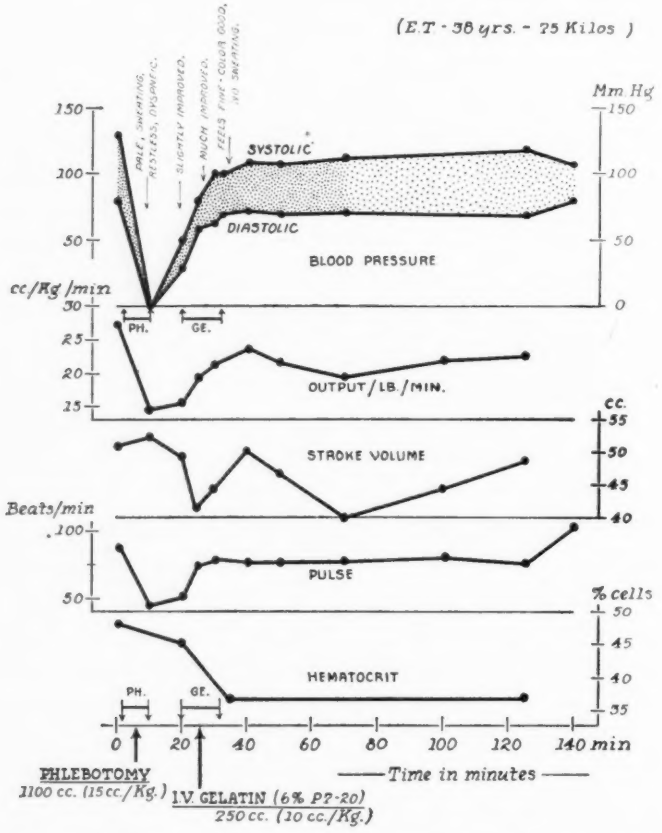

Fig. 3.—Gelatin replacement in acute experimental hemorrhage.

ulcer was made. Gelatin was available before either plasma or whole blood could be obtained and she was given 250 c.c. of 6 per cent gelatin solution in forty minutes. At that time her blood pressure was 74/48 and pulse 128, and gelatin was discontinued because it was expected that the pressure would continue to rise as the blood volume increased and it was thought undesirable to raise the systolic pressure over 90 mm. of mercury. A whole blood transfusion was begun one hour later when the pressure was 88/58 and the patient had an immediate reaction with a chill and vomiting (Fig. 4).

A 30-year-old Negro with a stab wound of the chest was admitted to a neighboring hospital and treated over a period of ninety minutes

with an intravenous drip of 800 c.c. of normal saline solution without any change in blood pressure, which remained at 60/40. Then 500 c.c. of 6 per cent gelatin solution were given intravenously with a rise in blood pressure to safer levels and a fall in pulse rate from 116 to less than 100, as illustrated in Fig. 5.

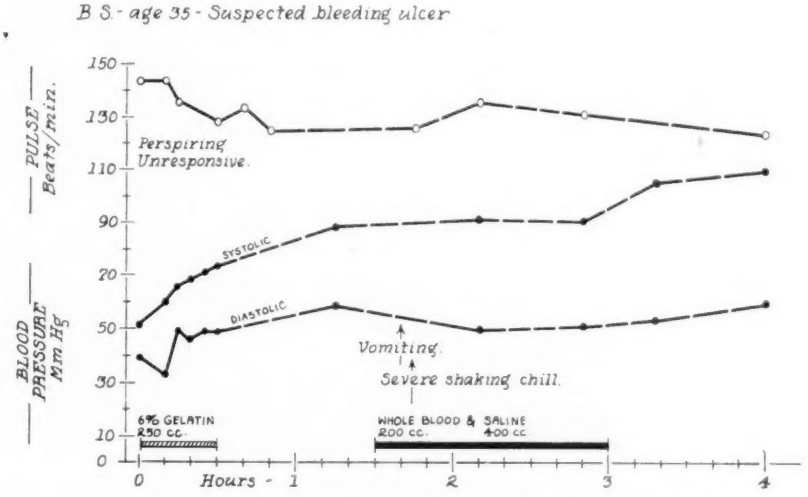

Fig. 4.—Treatment of hemorrhagic shock with gelatin.

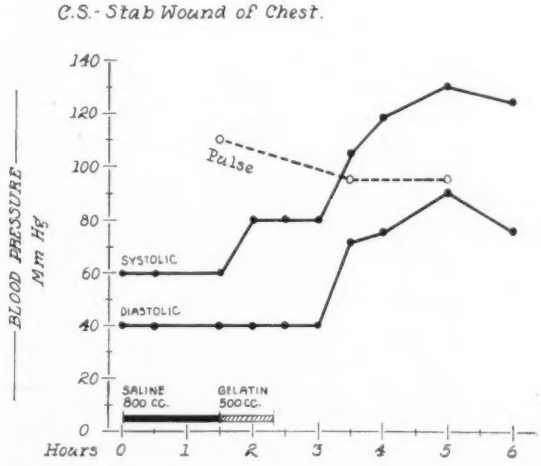

Fig. 5.—Treatment of traumatic shock without evidence of blood loss with gelatin.

A 52-year-old Italian in profound shock was admitted after a severe hemorrhage from a wound in the femoral vein. He presented the usual picture of shock except that his pulse was not rapid and his respirations were of the Cheyne-Stokes variety. He appeared to be at the point of death. By means of two simultaneous infusions, 1,000 c.c. of 6 per cent gelatin solution were given in thirty minutes with rather a remarkable response (Fig. 6).

The fourth patient was a volunteer who was bled 1,100 c.c. in eight minutes. His response to gelatin is illustrated in the section on Acute Experimental Hemorrhage With Gelatin Replacement.

In these four patients treated with gelatin, the infusions were received smoothly and gelatin was thought to be equal to plasma in every way. None of these patients had any unpleasant reactions to gelatin although one did to subsequently infused whole blood. In two of the three emergency cases, gelatin was available for use before plasma could be obtained from the blood bank.

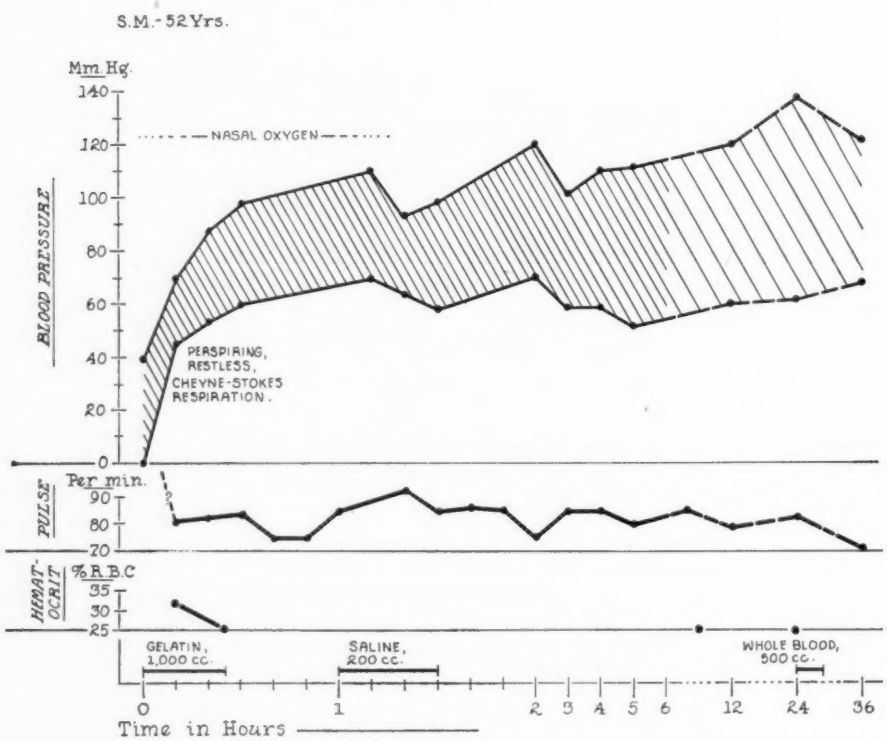

Fig. 6.—Treatment of hemorrhagic shock with gelatin.

Fluid Balance.—Fluid balance studies were done on fourteen patients in whom we attempted to produce a diuresis. Thirteen of these patients had edema associated with low serum proteins or had ascites. One patient had become anuric following a transfusion reaction. Urinary output thereafter was very low in spite of glucose and plasma infusions and the use of diuretics. Following gelatin infusions the output increased progressively after each of three daily infusions until it was over 2,000 c.c. per day. He continued to have an excellent output but succumbed with a mounting blood urea nitrogen level.

In patients with ascites we were not able to produce more than a transient diuresis and were not able to improve their symptoms. In

fact, several became more uncomfortable during the period when they were receiving gelatin.

In patients with cardiac edema, of course, gelatin is definitely contraindicated because of the patient's inability to cope with the increased blood volume.

Several patients with massive anasarca which developed terminally in the course of generalized carcinomatosis or lymphosarcoma showed a diuresis and loss of weight after receiving gelatin. Although the general course of these cases was unaffected, one patient, with edema so extensive that he could not close his hand, experienced remarkable temporary improvement.

It was in two patients with nephrosis without active nephritis that the most striking favorable results were obtained. One, a 38-year-old Negro (Table V), had only ankle and facial edema but was unable to walk more than 100 yards before his feet became so swollen and painful that further activity was prevented. After each of several gelatin infusions of 1,000 c.c., the patient had a diuresis and was able to walk a distance of four miles on several occasions. His ability to walk diminished gradually over a period of three to five days following infusion, a period corresponding to the disappearance time of the circulating gelatin.

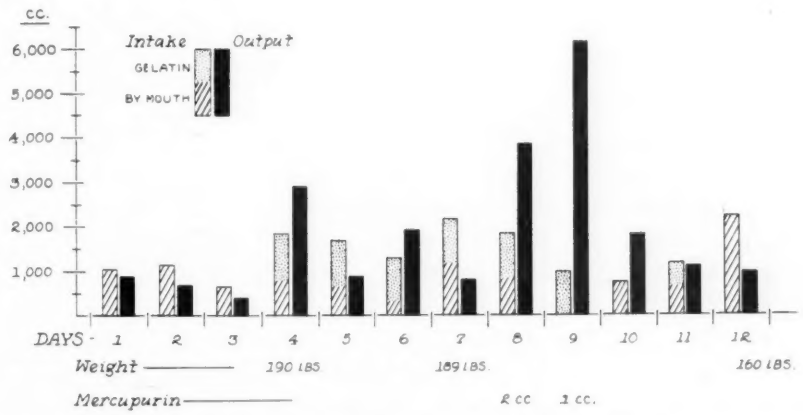

Fig. 7.—Fluid balance in the nephrotic stage of glomerulonephritis with repeated infusions of gelatin.

The other nephrotic patient had a diuresis following daily gelatin infusions but finally rid himself of edema and lost twenty-nine pounds after the administration of mercupurin with gelatin. This combination produced a better diuresis than was obtained with either alone or with other intravenous solutions when he was in a comparable condition (Fig. 7).

Patients with active nephritis in an edematous state apparently derive no benefit from intravenous gelatin.

Histologic Examination of Autopsy Material.—Fourteen patients who had received gelatin infusions subsequently died of their respective diseases and autopsies were obtained on all of them. Gelatin had been given from three hours to six weeks prior to death.

The tissues of eight of these patients have been carefully examined.* In general the interpretations are in conformity with Ratcliffe's detailed analyses of histology of dog tissues after gelatin infusion.[9] There is no evidence of chronic liver damage with storage of gelatin in the liver or any other organ. All the tissue changes in the liver, kidney, adrenals, and lungs are apparently reversible and are similar to those found in the dog after infusions of gelatin or plasma.

SUMMARY AND CONCLUSIONS

1. Ossein gelatin especially prepared for intravenous use in 4 per cent and 6 per cent solutions can be administered easily and safely. Clinical experience with 190 infusions of gelatin totaling 132 liters given to 100 patients is the subject of this report.

2. No untoward reactions attributable to gelatin per se were encountered with one exception and that in a man who had previously reacted unfavorably to infusions of blood, plasma, glucose and saline solutions, 2 per cent saline, and amino acids.

3. Following major operative procedures, the administration of gelatin produces a favorable response similar to that observed with plasma transfusion.

4. Nine patients given repeated infusions of gelatin at intervals of at least fourteen days after the previous infusion exhibited no anaphylaxis.

5. The increase in the erythrocyte sedimentation rate which follows the infusion of gelatin is related to the phenomenon of pseudoagglutination of erythrocytes. No increase in clotting time was observed in seven patients after gelatin infusion.

6. No bromsulphalein retention was observed after single or repeated infusions of gelatin solutions in seventeen patients.

7. There is no evidence of any permanent change in renal function, as determined by urea clearance, after gelatin infusion even with the administration of large amounts to patients with pre-existing renal damage.

8. Following the infusion of gelatin there is a depression of the serum protein concentration which cannot be accounted for by hemodilution as measured by hematocrit. The decrease involves the albumin, globulin, and fibrin fractions but is most marked with fibrin. There is a reciprocal relation between the concentration of the serum proteins and the circulating gelatin, the latter disappearing from the blood stream in three to five days.

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*Examination by Dr. Herbert R. Ratcliffe of the Department of Pathology, School of Medicine, University of Pennsylvania.

9. Elevation of venous pressure following the infusion of gelatin was consistently observed. There is no apparent relationship between the venous pressure rise and the volume or rate of infusion. There is a fairly consistent correlation between the increase in venous pressure and the decrease in hematocrit.

10. Cardiac output, as measured by the ballistocardiograph, was consistently increased after infusions of 750 to 1,000 c.c. of a 6 per cent gelatin solution. The increase reached a maximum three to four hours after infusion and returned to normal within twenty-four hours.

11. In acute experimental hemorrhage in voluntary human subjects, the replacement of two-thirds of the volume of blood removed with a 6 per cent gelatin solution corrected changes in blood pressure, venous pressure, pulse, stroke volume, and cardiac output secondary to blood loss.

12. Gelatin solutions are effective in the treatment of at least the early phases of hemorrhagic shock.

13. In certain types of edema there is a diuresis following the administration of gelatin solutions which is accompanied by clinical improvement.

14. Further studies on the value of gelatin in shock, burns, and hypoproteinemic states are clearly warranted.

15. Histologic examination of the tissues of eight patients who died of their respective diseases at intervals varying from three hours to six weeks after receiving gelatin revealed no evidence of gelatin storage in the tissues or of irreversible tissue change.

The authors wish to express their sincere appreciation to Miss Rozanne Peters and to Miss Louisa Bullitt for their invaluable assistance.

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EFFECT OF DICUMAROL ON SUSCEPTIBILITY TO ACTION OF HEPARIN

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HEPARIN acts as an antiprothrombin and in the presence of blood plasma as an antithrombin. Susceptibility to the action of heparin should be related to the amounts of prothrombin and thrombin in the circulation. As the thrombin is formed from the prothrombin a substance such as 3,3′-methylene-bis-(4-hydroxycoumarin) (dicumarol)[1-4] capable of causing a drastic reduction in prothrombin might be expected to increase susceptibility to the effect of heparin.

In the dog, Bollman and Preston found this effect did not materialize.[5] They stated that the rate of disappearance of heparin from the blood and its effectiveness in decreasing coagulability of the blood were not materially different in dicoumarinized dogs and in normal animals.

In patients, however, we have found that the effect of heparin is enhanced by the administration of dicumarol when the latter is given in fairly liberal amounts. The expense of heparin has been one of the factors limiting its use, yet for many purposes heparin remains the drug of choice for anticoagulant therapy. A less expensive adjuvant permitting the use of smaller amounts of heparin in achieving an anticoagulant effect would be desirable.

A study of the synergism of these drugs has therefore been carried out on a considerable group of patients requiring anticoagulant therapy.

METHODS

Coagulation time was determined by the Lee-White technique.[6] One cubic centimeter of venous blood was placed in each of three corked test tubes of 8 mm. bore. Tube number one was tilted at one-minute intervals until blood no longer flowed up the side of the tube. The process was then repeated with tube number two and then with tube number three. The interval of time from the placing of the blood in the tubes to the time of coagulation in the third tube was taken as the coagulation time. This ranged from twelve to eighteen minutes in normal individuals.

Prothrombin was determined by the method of Quick.[7] The normal controls ranged between twelve and fifteen seconds.

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Heparin was given in divided intravenous, intramuscular or subcutaneous injections in amounts adequate to maintain an average coagulation time of thirty to fifty minutes (the total amount being adjusted to each individual case).

Dicumarol was administered orally, in doses of 300 mg. the first day and 200 mg. the second day. Thereafter, the daily dosage was regulated by daily determinations of the prothrombin time. The prothrombin concentration was kept between 20 and 30 per cent of normal.

Three groups of patients were studied. They ranged in age from 17 to 70 years. Their diseases included thrombophlebitis, pulmonary embolism, thromboangiitis obliterans, peripheral arterial embolism and thrombosis, and retinal vessel thrombosis.

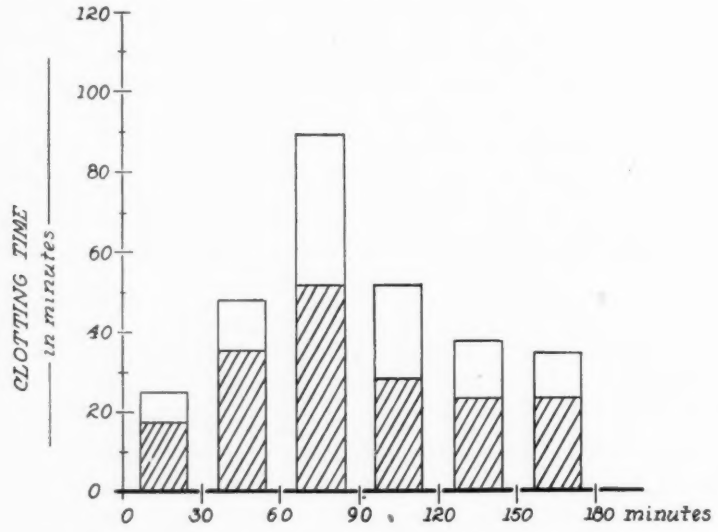

Fig. 1.—The white columns indicate the mean increase in the venous coagulation time in the coumarinized patient following the intramuscular injection of 5,000 Toronto units of heparin.

Group 1 consisted of thirty-one patients who received heparin and dicumarol simultaneously for a period of two to three weeks. Heparin was usually given intramuscularly because of a slow even rate of absorption. Clotting times were observed at the beginning of treatment after the injection of a fixed dose of heparin and then after the patient had been coumarinized the response to a second dose of heparin was measured.

Group 2 consisted of ten patients who received only heparin for the same period of time. Again coagulation times were observed after injection of a test dose of heparin at the beginning and end of treatment.

Group 3 was comprised of four patients who received only dicumarol over their period of treatment. Coagulation time was again observed after test doses of heparin at the beginning and end of the treatment period.

DATA

In the first group there was a definite increase in the susceptibility to heparin action in the coumarinized patient (Table I). The coagulation time was elevated to a greater extent and for a longer period of time as shown graphically in Fig. 1. In general the coagulability of venous blood had returned to normal in the noncoumarinized individual within two to two and one-half hours after an intramuscular injection of 5 c.c. of heparin (5,000 Toronto units). In the coumarinized

TABLE I

		BEFORE COUMARINIZATION						AFTER COUMARINIZATION					
			CLOTTING TIME IN MINUTES						CLOTTING TIME IN MINUTES				
			MINUTES AFTER INJECTION OF HEPARIN						MINUTES AFTER INJECTION OF HEPARIN				
PATIENT	DOSAGE (C.C.)	PROTHROMBIN % OF NORMAL	0 MIN.	30 MIN.	60 MIN.	90 MIN.	180 MIN.	PROTHROMBIN % OF NORMAL	0 MIN.	30 MIN.	60 MIN.	90 MIN.	180 MIN.
E. McG.	5 I.M.	90	10		45		10	20				60	45
J. K.	5 I.M.	95	15		50			35	15		70		
H. B.	5 I.M.	95	12		40	20		30	15		70	50	
L. J.	5 I.M.	90	15		50	20		35	18		75	45	
M. B.	5 I.M.	95	10		50		10	20	15		90		30
E. B.	5 I.M.	95	15		45	15		40	18		70	30	
S. L.	2 I.V.	90	20	180	100	25		20	23		180	40	
A. G.	2 I.V.	95	15	125	90	30		15	20		120	50	
A. K.	5 I.M.	95	12	30	45	25		20	15	40	90	40	
A. C.	1 I.V.	95	12	85	60			40	12	50	90		
W. M.	1 I.V.	95	12		80	30		40	12		90	50	
B. S.	5 I.M.	90	20	40	60			40	20	55	90		
G. C.	5 I.M.	95	20	40	50			40	20	50	90		
E. B.	5 I.M.	95	20	40	55	30		40	24	50	90	45	
T. V.	5 I.M.	95	18	35	48	30		30	23	45	90	50	
A. Q.	5 I.M.	95	20	35	45			15	25	60	100	60	
N. L.	5 I.M.	90	20	40	50			40	20	50	100		
J. L.	5 S.C.	95	15		40			50	18		70		
I. L.	1 I.V.	95	15		60	30		35	20		90	40	
I. H.	5 S.C.	95	15		25			25	20		60		55
J. H.	1 I.V.	95	20		65	35		40	20		90	45	
A. C.	5 I.M.	95	15		50			20	27		75		50
M. B.	5 I.M.	95	8	10	15		15	20	15	45	70		30
A. L.	5 I.M.	95	15	45	50	30		20	22	60	100	60	
R. J.	1 I.V.	95	15	80	45			35	20	45	80	50	
T. H.	5 I.M.	95	15	35	45	35	15	20	24	40	75	40	25
T. A.	5 I.M.	95	15	35	50	30		15	25	45	90	50	30
C. F.	5 S.C.	95	18	35	45	30		15	24	40	90	45	
E. F.	5 I.M.	95	18		50	30		15	20		90	45	
A. C.	5 I.M.	95	15	35	45	30		20	20	40	70	40	
S. F.	5 I.M.	95	15	30	45	30		25	25	45	85	40	
B. P.	5 I.M.	95	20		55	40		15	25		90	50	

	TIME AFTER INJECTION OF HEPARIN (MIN.)	CLOTTING TIME IN MINUTES	
		BEFORE COUMARIN	AFTER COUMARIN
Average for all patients receiving 5 c.c. I.M.	30	35	48
	60	47	84
	90	28	47
	180	13	35

individual with a prothrombin level of 20 to 30 per cent of normal, the coagulation time did not return to normal until six to eight hours after injection of the same dose of heparin. Approximately 40 c.c. of heparin (by the intramuscular route) would be required in the non-coumarinized individual to maintain the coagulation time around an average of thirty minutes for a twenty-four-hour period. In the coumarinized individual with a prothrombin time of 20 to 30 per cent of normal, the same effect was achieved with 15 to 20 c.c. of heparin.

There was a slight elevation of coagulation time in the coumarinized individual. This increase was seldom beyond the upper limits of normal unless the prothrombin concentration was reduced below 5 per cent of normal.

In the control Group 2 it will be seen that the effect of the test dose of heparin was essentially the same at the beginning and end of treatment (Table II). The base line coagulation time was increased very slightly if heparin was administered over a three-week period or longer, but this had no effect on the reaction to the test dose of heparin. Base line prothrombin times were unaltered. There was a slight increase in the prothrombin time immediately after an injection of heparin but this was of very short duration. However, intense heparinization showed a considerable effect on the prothrombin time. The twenty-four-hour heparin requirements of this group were essentially the same at the end of treatment as at the beginning, i.e., about 40 c.c. (by the intramuscular route).

Group 3 would indicate that the increased sensitivity to heparin is the result of dicumarol administration alone and is not due to the simultaneous administration of heparin and dicumarol over a long period of time (Table III). Patients showed the same increase in sensitivity and decrease in twenty-four-hour requirements as the patients in Group 1.

TABLE II

		BEGINNING THERAPY										ENDING THERAPY									
PATIENT	DOSAGE (C.C.)	0 MIN.	PROTHROMBIN TIME	30 MIN.	PROTHROMBIN TIME	60 MIN.	PROTHROMBIN TIME	90 MIN.	PROTHROMBIN TIME	180 MIN.	PROTHROMBIN TIME	0 MIN.	PROTHROMBIN TIME	30 MIN.	PROTHROMBIN TIME	60 MIN.	PROTHROMBIN TIME	90 MIN.	PROTHROMBIN TIME	180 MIN.	PROTHROMBIN TIME
G. W.	2 I.V.	15	80	110		80	65	30	80			20	80			80	70	30	80		
M. C.	1 I.V.	20	90	110	85	100	75			20	90	24	90	110	85	95	85			20	90
M. W.	5 I.M.	15	90	35	80	55	80	30	90			15	90	35	80	35	85	30	90		
V. C.	5 I.M.	15	90			40	85	30	90			15	90			40	80	30	90		
J. T.	5 I.M.	25	90			50	80	60	85	25	90	28	90			50	75	55	90		
I. L.	5 I.M.	20	95	40	85	50	85	35	95			24	90	40	80	50	74	35	90		
C. C.	5 I.M.	12	90			45	80			15	90	25	90			45	85			25	90
F. L.	5 I.M.	20	90			55	85	30	90			28	90			55	80	30	90		
V. A.	5 I.M.	20	95			60	80	45	90			20	95			60	80	40	95		
H. J.	5 I.M.	12	95	40	85	40	85					20	95	40		50	80		95		

TABLE III

		BEFORE COUMARINIZATION										AFTER COUMARINIZATION									
PATIENT	DOSAGE (C.C.)	0 MIN.	PROTHROMBIN TIME	30 MIN.	PROTHROMBIN TIME	60 MIN.	PROTHROMBIN TIME	90 MIN.	PROTHROMBIN TIME	180 MIN.	PROTHROMBIN TIME	0 MIN.	PROTHROMBIN TIME	30 MIN.	PROTHROMBIN TIME	60 MIN.	PROTHROMBIN TIME	90 MIN.	PROTHROMBIN TIME	180 MIN.	PROTHROMBIN TIME
C. V.	1 I.V.	15	95			40	80	30	90			15	30			100		50			
F. K.	5 I.M.	25	95	25	85	25	85	25	90	25		20	50	30	40	40	40	30	50		
J. H.	5 I.M.	12	90	35	80	45	85					20	30	50	20	90	25	60	30		
S. H.	5 I.M.	15	95	25	80	30	75	20	95			25	40	45	30	90	30	60	40	35	40

SUMMARY OF DATA

The results obtained indicate that when the prothrombin time is depressed to 20 to 30 per cent of normal by the oral administration of dicumarol, considerably greater effect is observed in a patient given a parenteral dose of heparin than in the noncoumarinized individual. Less heparin is needed to produce a given effect in the coumarinized than in the noncoumarinized individual (Fig. 1). Averaging the observations made, only one-half to one-third the amount of heparin was required when dicumarol was used.

DISCUSSION

In a previous communication with Panzer[8] we pointed out that the effects of heparin and 3,3′-methylene-bis-(4-hydroxycoumarin) were complementary.[8]

Heparin is found in animal tissues and was discovered to be the cause of the decreased coagulability of the blood in peptone shock.[9, 10] Heparin was finally isolated in form pure enough for administration to human beings in 1933, by Charles and Scott.[11] The substance is active only when given parenterally and takes effect immediately on entering the blood stream. The effect is short in duration in vivo although somewhat longer in vitro. Action is mainly on the coagulation time, by virtue of being an antithrombin as well as an antiprothrombin. Parenteral administration of protamine counteracts the effects of heparin. Despite recent advances in methods of manufacture, heparin remains relatively expensive.

Dicumarol was discovered to be the active principle in spoiled sweet clover hay which caused "sweet clover" disease in cattle.[1-4] It is a white crystalline substance which is active when given orally and may also be given parenterally. Dicumarol reduced the effective concentration of prothrombin. The effect is only evident twenty-four to forty-eight hours after administration and lasts for three or more days. Dicumarol is only active in vivo. The best antidote to its action is the

transfusion of fresh whole blood. Dicumarol is not on the market, but its manufacture is said to be inexpensive.

We are not yet certain that coumarin can supplant heparin in the prevention of thrombosis in man. In spite of the ingenious experiments of Bingham, Meyer, and Pohle,[12] and those of Bollman and Preston,[5] it is difficult to feel the same confidence in an anticoagulant that affects the prothrombin time as in one that affects venous coagulation time. The clinical reports, especially that of Barker, Allen, and Waugh,[13] have convincingly established its value in the prophylaxis of postoperative embolism. Probably it cannot supplant heparin for certain purposes. In the treatment of pulmonary embolism, prevention of propagation of the clot is of primary importance. The action of dicumarol is too slow. An agent is needed which will render the blood practically incoagulable at once. For this purpose an injection of 3,000 to 5,000 Toronto units of heparin intravenously (undiluted) is ideal. The same is true in many other types of embolism and thrombosis.

In vascular surgery it is advantageous to work in a field in which the coagulability of blood is normal and yet be able to reduce its coagulability sharply to prevent thrombosis as soon as the vascular tree is repaired. In this clinic heparin has been used repeatedly immediately following embolectomy for peripheral embolism[14, 15]

The current technique of anticoagulant therapy on Service B at the Hospital of the University of Pennsylvania may be described as follows:

An initial dose of heparin is given intravenously. At the same time 300 mg. of dicumarol are given orally. Additional heparin is given by a continuous intravenous drip or intramuscular injection every six hours. If the intramuscular route is chosen it is wise to select a preparation that does not contain an irritating preservative. Two hundred milligrams of dicumarol are given the second day and dosage is controlled thereafter by daily determination of the prothrombin time.

The dose of heparin usually approximates 15,000 to 20,000 units per day. It is adjusted to maintain a coagulation time of thirty to sixty minutes in patients with embolism. In patients requiring less drastic therapy or in whom there is serious danger of hemorrhage, the dose is reduced so that coagulation time is maintained at lower limits. This regime is usually continued for ten to fourteen days. The continuous use of dicumarol for over three weeks has sometimes been followed by hemorrhagic phenomena even though the prothrombin level is no lower than usual.

CONCLUSIONS

In man, administration of 3,3′-methylene-bis-(4-hydroxycoumarin) in amounts sufficient to reduce the plasma prothrombin concentration to 20 to 30 per cent of normal increases the sensitivity of the individual to heparin.

The synergism of the two drugs may be used to reduce the amount of heparin needed. Intramuscular administration of heparin is made practical, allowing a prolonged, evenly maintained increase in blood coagulation time. The inconvenience of maintaining a continuous intravenous drip is avoided.

When combined therapy is used, care should be exercised to avoid extreme anticoagulant effects which might result in hemorrhage.

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Erratum

On pages 408 and 409 of the March, 1944, issue of the JOURNAL in the article "The Use of Phlebography and Lumbar Sympathetic Block in the Diagnosis of Venospasm of the Lower Extremities" by E. M. Papper, M.D., and Allison E. Imler, M.D., Palm Springs, Calif., Fig. 7*B* and Fig. 8 should be interchanged.

Editorial

The Society of University Surgeons

THE widespread changes in the resident staff organizations of the hospitals of this country, necessitated by the war, have profoundly affected postgraduate training in surgery. The resident system, prior to the war, was regarded as a "royal road" to surgery. This program provided for an internship to be followed by periods in research work, as surgical pathologist, assistant resident, and finally resident surgeon. In the latter capacity the aspirant had the responsibilities of a service of his own and acquired not a little operative experience. There was, and probably still is, a question in some quarters as to the merits of this system—certainly it is not the only scheme for the adequate training of surgeons. However, the resident system does provide for a broad and definite program and the number of those seeking such training was always considerably greater than the number of posts available. During the prewar years the resident system was becoming more widely adopted as time went by.

The problems of the future are such that a rapid return to the prewar systems and programs of education, and training can hardly be envisaged. Those in the Armed Forces desiring further training will receive special consideration and the programs in teaching centers will have to be modified again to meet these conditions making adjustments for the different age groups and for previous experience. Emphasis will have to be placed upon condensation of training, not at the undergraduate level as is the case at present but at the postgraduate level, which now receives little attention. It appears, therefore, that the long periods of resident training may not be easily reinstituted and indeed this may not be possible for a long time.

The Society of University Surgeons was founded in 1938 and one of its principal objectives was the "development of methods of graduate teaching of surgery with particular reference to the resident system." Its membership is composed of exresidents who are actively engaged in the teaching of surgery. The majority of this group, however, are now in military service but they remain keenly interested in the problems of surgical training. It is hoped that their experiences during this war will find expression in some way at the proper time, and that these experiences may be given due consideration in the formulation of plans for the training of surgeons in the future.

—*Alexander Brunschwig, M.D.*
Chicago, Ill.

Review of Recent Meetings

MEETING OF THE SOCIETY OF UNIVERSITY SURGEONS

CLARENCE DENNIS, M.D., MINNEAPOLIS, MINN.

THE annual meeting of the Society of University Surgeons was held in Nashville, Tenn., Feb. 10, 11, and 12, 1944. The Society members were the guests of the Vanderbilt Hospital group and were very cordially entertained.

On the morning of the first day of the meeting, a series of papers was presented by members of the staff at Vanderbilt University. The group was welcomed by **Dean W. S. Leathers,** who made a plea that members of the organization take a more active part in the formation of legislation to be anticipated in the near future having a bearing on the practice of medicine. **G. John Buddingh** gave a presentation on a type of ratbite fever on which he is making studies. **G. Sidney McClellan** spoke concerning experiences with continuous caudal anesthesia in obstetrics and gynecology. He seemed to be particularly impressed with lack of evidence of asphyxia in the newborn infant when such type of anesthesia was used. The blood loss apparently was less under these circumstances also. **James Ward** made a very interesting presentation on the effects of rapid compression waves on animals partially and completely submerged in water. **J. K. David, Jr.,** spoke about splenectomy in hemolytic anemia in infancy. He stressed that determination of increases in serum hemoglobin by the use of a benzidine quantitative test seemed to be a very sensitive means of diagnosing the condition and presented the case of an infant who presented a high serum hemoglobin level and a normal fragility test. The infant was cured by splenectomy. **A. S. Minot** discussed the chemistry and clinical applications of the serum tocopherols in muscular dystrophy, presenting some reasons for the clinical failure of vitamin E therapy. **M. T. Bush** talked about flavicin, an antibacterial substance from *Aspergillus flavus.* The isolation of this material is similar to that of penicillin. It is toxic to animals, but the toxic factor apparently can be separated from the flavicin. This material apparently offers complete protection of mice against the pneumococcus and is about one-fourth as active as the most active preparations of penicillin. **Paul Hahn** discussed the use of radioactive isotopes in medicine, spending considerable time on studies on the absorption and utilization of ferrous iron as against ferric iron. He showed that ferrous iron is two or three times as much absorbed as ferric iron in the iron deficiency anemias; and the utilization, therefore, is much more quick and effective. **George R. Meneely** discussed the laboratory evaluation of pulmonary function. He stressed the value of a knowledge of the "breathing reserve" which is the difference between the vital capacity and the tidal air at rest. **Smiley Blanton** talked about the relation of psychiatry to surgery, giving several examples of cases in which an alert attitude as far as the psychiatric status of the patient was concerned was very helpful. **W. F. Meacham** presented a paper on intrathecal penicillin therapy of experimental staphylococcal and pneumococcal meningitis. The study was undertaken because of the finding that penicillin given intramuscularly or intravenously reaches the spinal fluid in much lower concentration than is found in the blood stream. The studies indicated that some value was derived from intrathecal administration of

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the drug. **William Frye** presented a very interesting talk and colored pictures concerning the problems of medical care in Central America.

At the afternoon meeting, February 10, two papers were presented which do not appear in this issue of the JOURNAL. The first of these was by **Alexander Brunschwig,** of the University of Chicago, on extending the surgical attack upon cancer of the colon. Brunschwig presented several cases in which radical surgery involving removal of other viscera such as segments of small intestine, dome of bladder, uterus, kidney, etc., was accomplished. Discussion of the paper by members of the group indicated that the general impression is that such extensive surgery is well worth while in cancers of the colon.

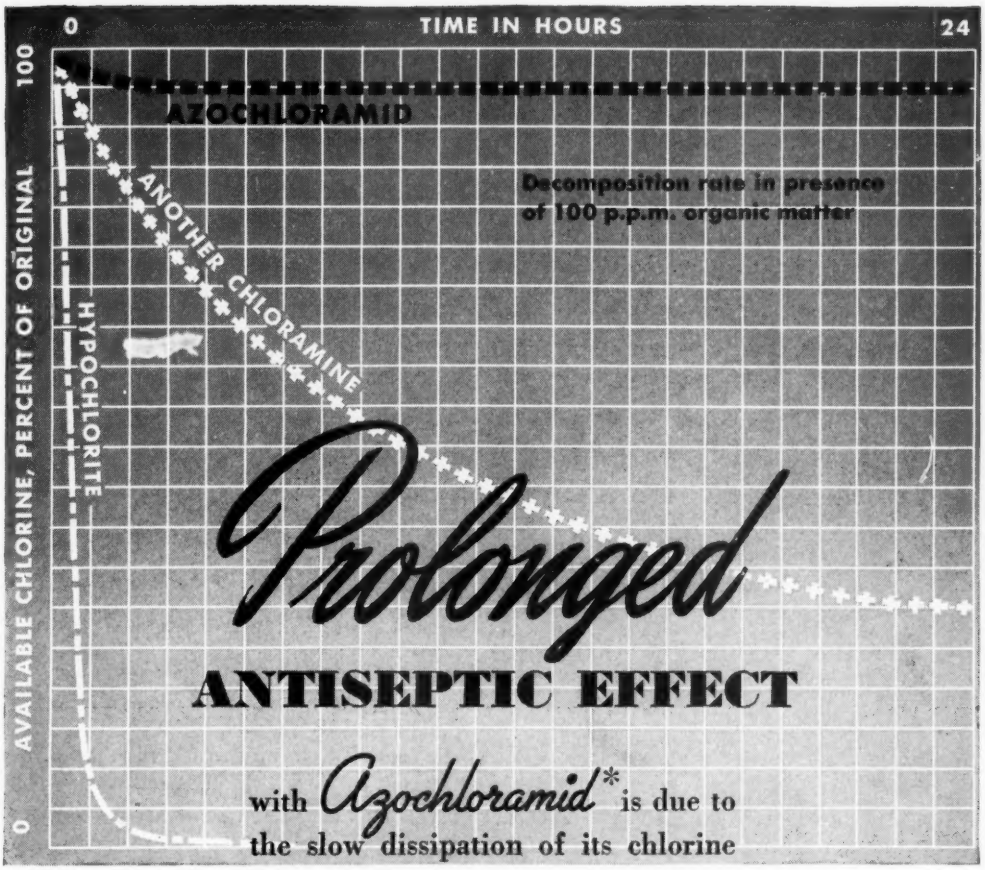
Lieutenant Colonel D. Henry Poer, of Atlanta, Ga., presented a case of primary adenocarcinoma of the appendix arising near the base of the organ with secondary acute appendicitis apparently on the basis of obstruction by the tumor.

On Friday morning, February 11, several papers were presented which will not appear in this issue of the JOURNAL. One by **John T. Reynolds** of Chicago concerned embolic occlusion of peripheral arteries. On the basis of the results in a series of cases, Reynolds concluded that the patient should be given heparin immediately in event of such embolic occlusion. In the lower extremity he had some success with operating upon the heparinized patient in the inguinal region, extricating the clots by instrumentation of the artery as exposed and opened. He wished particularly to warn against the use of sympathetic block in arterial occlusions of the lower extremity because of the risk of passage of the emboli to lower vessels which could not be easily reached. Embolectomy should be done as soon after embolic occlusion has occurred as is possible. In the shoulder, on the other hand, the combination of heparin and sympathetic block appears to be in order because of the good collateral circulation available. In the discussion of this paper **Jonathan Rhoads** stated that **Ravdin** has devised an instrument like a corkscrew on the end of a long slender rod which can be passed up the iliac artery for the purpose of grasping and withdrawing emboli. **Barney Brooks** pointed out that it is of great importance to keep the extremity constantly moving postoperatively to avoid thrombosis of collateral vessels. In answer to questions, **Reynolds** stated that he had no trouble with postoperative bleeding even though operation was done on heparinized patients.

William J. German and **Bernard S. Brody** discussed compound craniocerebral injuries.

Papers presented by **H. P. Jenkins** and **J. G. Allen** and by **K. W. Thompson, J. S. Horsfall,** and **G. A. Zentmeyer** are being published in full elsewhere, and are therefore not abstracted here.

Throughout the meetings the Nashville group was most cordial to the members of the society, and we would like to express once again our appreciation of the hospitality shown us.



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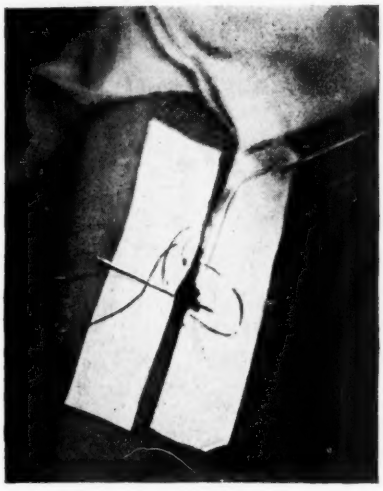

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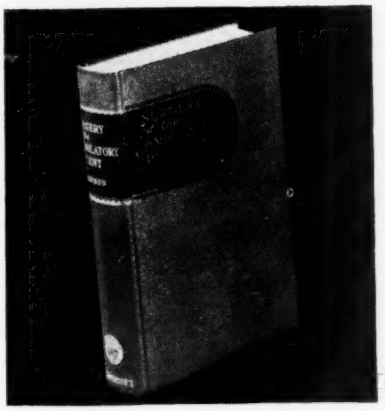

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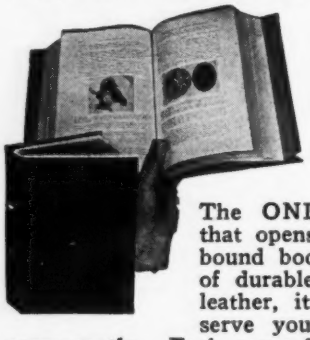

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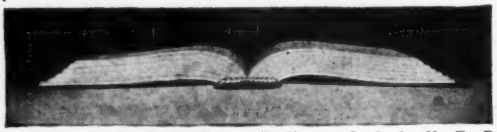

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